Effect of Intranasal Estrogen on Vocal Quality

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Summary: The objective of this study was to evaluate the effect of intranasal estrogen therapy on female vocal quality. Thirty-two women who had surgically induced menopause were included into the study group and examined through hall year for this study. Estrogen treatment was proposed to all of the patients. Twenty-three of them accepted the treatment protocols including oral (n = 12) (2 mg estradiol; Estrofem; Novo Nordisk, Denmark) and intranasal (n = 11) (300 mcg 17beta-estradiol; Aerodiol; Servier, Chambray-les-Tours, France) form of estrogen. The rest of patients refused estrogen treatment and those patients constituted the control group (n = 9). Vocal changes were evaluated with Voice Handicap Index (VHI) and acoustic analysis of voice variations (fundamental frequency [F0], SD F0, jitter, shimmer, normalized voice energy, and harmonics-to-noise ratio) at baseline and after 1-year follow-up. According to VHI, while voice improvement was not clear in oral estrogen group, it was significant at intranasal estrogen group. Voice quality in patients treated with hormone replacement therapy (HRT) was significantly higher than patients without HRT. But between two treatment groups, there were no any statistical discrepancy. According to acoustic analysis, vocal stability among the women who use HRT was significantly better than those who did not use. Intranasal estrogen exerted the most significant effects on vocal stability. The data of our study support that voice undergoes changes in lack of estrogen in surgically induced menopausal women. Taken together with the relevant studies, while oral estrogen replacement therapy shows a favorable influence on voice quality, it seems to be more pronounced with intranasal estrogen than oral form.

Key Words: Estrogen–Hormone replacement therapy–Voice quality–Voice analysis.

INTRODUCTION

It is assumed that human larynx is a sensitive target organ for steroid hormones. For both male and female genders, the voice alters from childhood to elderly under the effect of estrogen, progesterone, and androgens.[1] Voice alterations in menopause and menstrual cycle are also assumed to be result of hormonal changes.[2–5] Voice alterations as side effects of hormonal therapy were reported in several recently published studies.[3,6–10] A significant number of those studies have been supported estrogen replacement therapy as it has a good impact on vocal cords.[6,7,11] However in few of them, voice changes in women treated with estrogen were supported by satisfactory objective voice analysis.[11–13] In this study, we investigated the effect of oral and intranasal form of estrogen therapy on vocal quality. Intranasal estrogen replacement therapy (intranasal 17-beta-estradiol) is a novel method for postmenopausal woman for hormone replacement. It has some superiority to other form of hormone replacement therapy (HRT). It was demonstrated that intranasal estrogen therapy caused a lower endometrial and breast tissue stimulation compared to the equivalent oral therapy.[14] We thought that intranasal form of estrogen may affect directly the vocal fold epithelium and may exert greater impacts on voice quality than systemic form of HRT. Hence, we evaluated the effects of intranasal estrogen on women vocal quality and compared with the effects of oral HRT.

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METHODS

Subjects and estrogen therapy

Our study group included 36 patients with whom underwent hysterectomy-oophorectomy, but four of them were excluded due to noncompliance with the study protocol or their treatment. Thus, analysis was performed on 32 surgically postmenopausal women ranging in age from 27 to 55 years (mean age, 46.8) who completed 1-year follow-up. The patients who had endometrial, ovarian, cervical, vaginal, or vulval cancers; or a family history of these cancers; or a history of hypertension, cardiovascular disease, or stroke were excluded from the study. Before treatment mammographies of patients were examined, revealed no abnormalities. The otolaryngologic examinations, which include flexible laryngoscopic examination and laryngostroboscopy, were performed to all patients. Patients with laryngeal lesion or voice pathology were excluded from the study. All participants had no history of formal singing or voice training, smoking, reported hormonal imbalances including thyroid hormones, and neurological problems. After obtaining the approval from our institutional review board and written consent from all participants, an initial screening was conducted. HRT was initiated 30 days after their operations. Intranasal form of estrogen (300 mcg 17beta-estradiol; Aerodiol; Servier, Chambray-les-Tours, France) was administered to 11 patients. Oral form (2 mg estradiol; Estrofem; Novo Nordisk, Denmark) was applied to 12 patients. All patients in HRT groups took their pills or pulse their spray daily. Nine of the participants refused to undergo HRT.

VHI and acoustic voice analysis

The Turkish version of Voice Handicap Index (VHI) was performed to all patients to evaluate their satisfaction objectively.[15,16] VHI was administered to patients 30 days after their operation concurrently with HRT and 12 months after

the therapy. VHI scores and three subscores (functional [F], physical [P], and emotional E]) were analyzed for all groups. Voice samples were taken from the subjects 24 hours before the initiation of HRT and at 12th month of treatment. Each participant was recorded three times during each interval. During the individual recording sessions, participants were instructed to sustain a vowel /a/ (as in "father") in isolation, three times for 3–5 seconds. For each recording session, the participant was seated in a quiet room; with a Shure SM 58 (SHURE Inc., Niles, IL, USA) headset–microphone attached approximately 5 cm away from her mouth. The signal was stored onto Platium Pro, USA digital data cartridges using Adobe Audition 1.0, USA digital audio tape recorder, with a sampling rate of 44.1 kHz and resolution of 16 bit. Following the recordings, each voice sample was stored and analyzed by the Dr. Speech Science program (DRS) (version 4.42 USB, Tiger DRS, Inc, Seattle, USA, 1998). Acoustic voice parameters: frequency and amplitude variations (jitter, shimmer, harmonics-to-noise ratio [HNR], normalized voice energy [NNE]), and fundamental frequency (F0), and standard deviation of F0 were measured. Control group similar to HRT-applied patients underwent same examinations at similar time durations.

Statistical tests

In all groups, basal and first year acoustic voice measurements were evaluated for testing normality with Kolmogorov-Smirnov test (KST) with Lillieffors correction. In all cases, the KST was also applied for testing normality between treatment and control groups. Data were found to be compatible with normal distribution ($P > 0.05$). Acoustic voice parameters were analyzed with paired *t* test. Comparisons among three groups were performed by the Kruskal-Wallis analysis of variance test. Perceptual and self-assessment data, before and after voice therapy, were compared using Wilcoxon's test and Student's *t* test. Correlations between the VHI domains were measured by means of Pearson's correlation coefficient. All statistical analyses were performed with SPSS for Windows 13.0.1 (SPSS Inc., Chicago, IL).

RESULTS

The patient characteristics were shown in Table 1. Age of patients was statistically similar in those three subgroups ($P > 0.05$). Patients in intranasal estrogen group sprayed their drug intranasally twice a day in regular time and patients in oral estrogen group have used their pills daily. All reported no omission in pill taking or spray pulsing during the time of the study.

Voice Handicap Index

All participants were completed the questionnaire before and after 1-year follow-up. In perceptual evaluation of their voices, all final scores were smaller than initials at treatment groups and higher than initials at no-HRT group (Figure 1). However, statistically significant improvement was observed only in intranasal estrogen group for total VHI scores ($P = 0.02$). While we look at subscores, main perceptual voice disturbances were belonging to *physical* group for all patients. Significant improvement in intranasal estrogen group ($P = 0.02$) and significant deterioration in no-HRT group ($P = 0.03$) were observed. Surprisingly, in oral estrogen group no statistically significant improvement was observed in total score and in any of subscores ($P > 0.05$).

A comparison between the groups for the results of VHI was made with Pearson's correlation test. Scores at both pre-HRT and post-HRT state were compared. Comparison of VHI scores at posttreatment state between oral HRT and intranasal HRT groups was statistically significant. It was observed in total scores (oral: $P = 0.03$, 95% confidence interval [CI] = 5.4–22.5 and $P = 0.02$, inhaler: 95% CI = 7.6–24.4) and *physical* subscores (oral: $P = 0.001$, 95% CI = 5.7–16.7 and inhaler: $P = 0.03$, 95% CI = 7.0–18.4). A marked deterioration of VHI, especially in *physical* domain was noted in patients without HRT. When we compare the pretreatment scores in those subgroups no statistically significant difference was observed ($P > 0.05$). After the treatment, we did not observe any difference between the domains of oral and intranasal estrogen group ($P > 0.05$).

Voice analysis

In all cases, voice records were obtained before and 1 year after the follow-up. All groups exhibited similar F0 at the beginning of the study and all of them were in the normal female mean F0 range.[4] Although it slightly decreased in no-HRT group and

TABLE 1.
The Patient Characteristics

Groups (n = 32)	Age ± SD	Pathology for Surgery	Type of Surgery
All HRT group (n = 23)	47.8 ± 4.9		
Inhaler (n = 11)	46.5 ± 5.5	Menometroragghia (n = 1) Uterine leiomyoma (n = 9) Benign ovarian process (n = 1)	TAH + BSO (n = 10) VH + BSO (n = 1)
Oral (n = 12)	48.2 ± 4.0	Uterine leiomyoma (n = 10) Uterine fibroid (n = 2)	TAH + BSO (n = 10) VH + BSO (n = 2)
No-HRT group (n = 9)	45.4 ± 7.9	Uterine leiomyoma (n = 8) Uterine fibroid (n = 1)	TAH + BSO (n = 9)

TAH + BSO: Total abdominal hysterectomy and bilateral salpingo-oopherectomy; VH + BSO: vaginal hysterectomy and bilateral salpingo-oopherectomy.

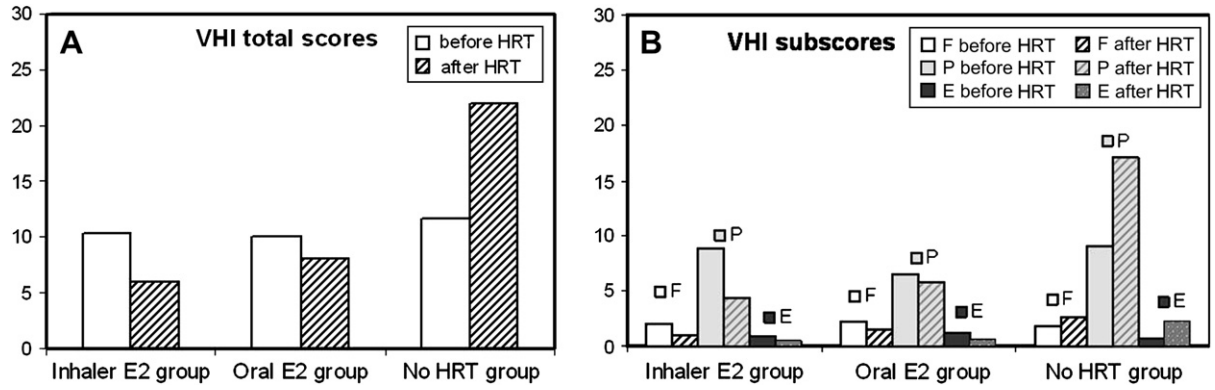

FIGURE 1. Voice Handicap Index (VHI) before and after hormone replacement therapy (HRT) or follow-up in three groups. **A.** Total scores, **B.** Subscores (F: functional, P: physical, E: emotional).

oral estrogen group, it tended to increase in intranasal estrogen group after 1 year. But the mean and standard deviation of F0 changes were not significant in any group (Figure 2). Compared to the end of the study results, jitter and shimmer were the most affected voice parameters during the study. Although jitter and shimmer parameters were elevated in no-HRT group, all were decreased in both HRT groups (Figure 3). But jitter and shimmer changes were statistically significant only in intranasal estrogen group ($P = 0.003$ and $P = 0.007$, respectively). Though there was an increasing tendency in NNE values and a decreasing tendency during study in no-HRT group, this was of no statistical significance. Similarly, both HRT groups exhibited lower NNE values and higher HNR values at the end of the study but changes were significant only in intranasal estrogen group for NNE values ($P = 0.033$) (Figure 4). Although the three groups were compared to one another for beginning voice values, we could not obtain any significant difference in any voice parameter. At the end of 1-year follow-up, F0, NNE, and HNR values were similar and not statistically different from each other. SD of F0, jitter, and shimmer values were marked improved in taking HRT groups compared to no-HRT group (for oral estrogen group; $P = 0.01$, 95% CI = 0.25–1.67; $P = 0.02$, 95% CI = 0.02–0.34; and $P = 0.003$, 95% CI = 0.46–2.02, respectively, and for intranasal estrogen group; $P = 0.03$, 95% CI = 0.43–1.87; $P = 0.009$, 95% CI = 0.06–0.39; and $P = 0.0001$, 95% CI = 1.23–2.8, respectively). Greater voice quality improvement was observed in intranasal estrogen group compared to oral estrogen group. Jitter and shimmer values were markedly smaller in patients who use intranasal estrogen than patients who use oral estrogen ($P = 0.009$, 95% CI = 0.01–0.07 and $P = 0.0001$; 95% CI = 0.48–1.06, respectively).

DISCUSSION

The deterioration of female voice after menopause was barely known since the 19th century, but the effect of estrogens on vocal quality was investigated after the late 20th century.[17] Although Frable[18] impressed the voice changes at premenstrual state due to hormonal changes at 1962, Silverman and Zimmer[19] and Brodnitz[20] reported the effect of menstrual cycle on voice quality in 1978 and 1979. Later on, several authors showed that hormonal changes at menstrual cycle or menopause caused voice alterations due to estrogen deficiency.[4–7]

Large numbers of studies concluded that female voice undergoes deterioration after natural or surgically induced menopause.[6,10,13] Abitbol et al[4] have explained these differences with "menopausal vocal syndrome." This syndrome characterized by loss of vocal quality due to lowered vocal intensity, decreased frequency range, and vocal fatique. These perturbational differences were due to vocal muscle atrophy and reduction in the thickness of the mucosa under the effect of hormonal changes.[4] Our findings were also similar. But bear in mind that voice change could be different in surgical or natural

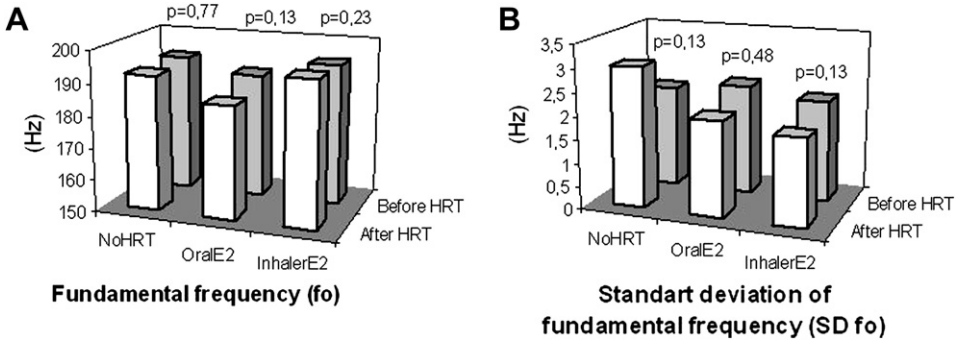

FIGURE 2. **A.** Mean fundamental frequency (F0) and **B.** Standard deviation of F0 (SD F0) before and after hormone replacement therapy (HRT) or follow-up in three groups.

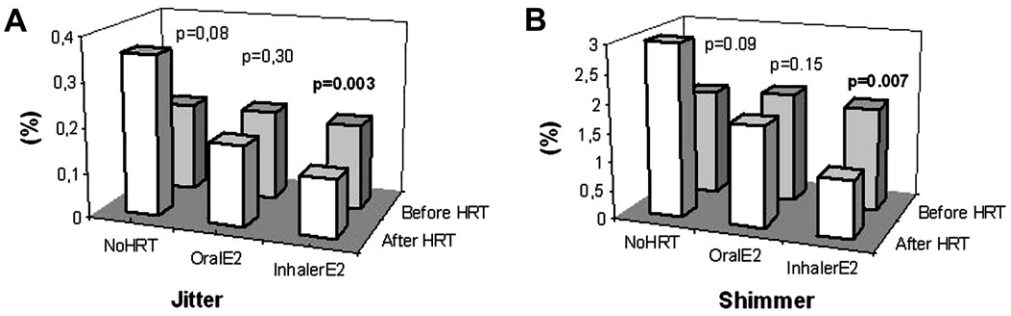

FIGURE 3. **A.** Jitter and **B.** Shimmer parameters before and after hormone replacement therapy (HRT) or follow-up in three groups.

menopause. As there may be continued androgen/estrogen production by menopausal ovaries, voice alterations could be better in natural menopause.

We observed significant deterioration in voice perturbation measurements after the first year of menopause. However, the results of patient's answered questionnaire (VHI) were not supporting the acoustic analysis. There are a couple of ways to explain the controversial results of VHI. First one, VHI has items belonging to functional, physical, and emotional subgroups. Menopausal vocal syndrome has complaints belonging to *physical* subgroup due to vocal atrophy and mucosal thickness. In our patients, most complaints consisted of a harsh and scratchy voice that belongs to *physical* domains. Therefore, results were statistically significant only in *physical* subscore. On the other hand, functional and emotional domains were almost in normal values. Similarly, Lindholm et al[7] administered a questionnaire to 42 postmenopausal women and they found out that the major complaint was increasing hoarseness after 10 months of follow-up. As only 10 of 30 questions were belonging to the *physical* status in VHI, total scores were not statistically significant at the end of the study in our patients. Therefore, total scores of VHI were not consistent with acoustic analysis results. We suggest that total scores of VHI could significantly change after long-term follow-up.

The effect of hormonal changes on the voice of healthy women was typically investigated during menopause.[2,7,11] Several authors demonstrated the influence of HRT on voice on surgically induced menopausers.[7,9,12,13] The current recommendation for women with early ovarian failure is estrogen-based HRT until the average age of the menopause to reduce the risk of osteoporosis and cardiovascular disease.[21] The most commonly used route is oral unless there is a preexisting medical condition. Parenteral delivery systems include patch, gel, subcutaneous implants, nasal spray, and vaginal ring. Aerodiol (17beta-estradiol) is a nasal spray form of estrogen replacement therapy.[14,22] It could directly stimulate the vocal cord epithelium via inhaler route. Studies have shown similar alterations between cytological smears of the vocal fold epithelium and cervical smears during the menstrual cycle. Human vocal cords epithelium has receptors for androgen, estrogen, and progesterone.[1,23] When this study was designed, we aimed to investigate the direct effect of estrogen on vocal cord epithelium. We assumed that Aerodiol could locally affect the vocal cords epithelium and improve vocal quality more than other forms of HRT.

Similar to previous reports, we obtained that oral HRT improved the vocal quality in postmenopause women. We also obtained that vocal quality was deteriorated in the group with no HRT. Lindholm et al[7] found the most significant worsening in F0 values. They have explained that the drop in F0 was associated with the lack of estrogen and an increase in the testosterone-estrogen ratio. Under the effect of high testosterone level, tissue structure of vocal cords alters and masculine voice characteristics occur. In our study, F0 changes were not statistically significant in any group. The most affected parameters were jitter and shimmer in our study. In a study with patients who used oral contraceptives and who do not, Amir et al[13] found that oral contraceptives improved the vocal quality. According to this study, the most affected parameters were also jitter and shimmer. They reported that there were no significant differences

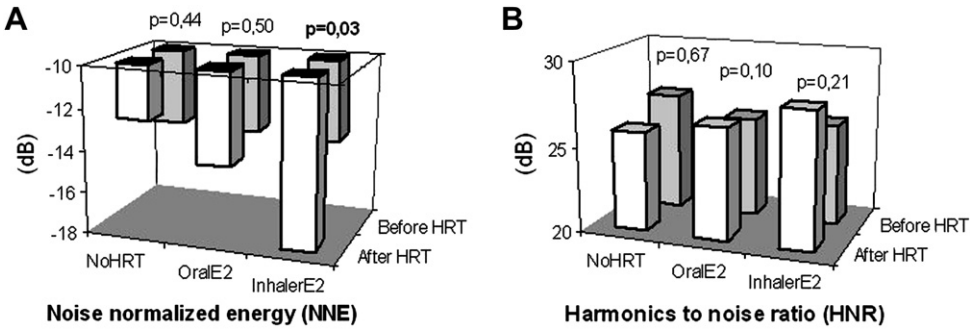

FIGURE 4. **A.** Noise normalized energy (NNE) and **B.** noise-to-harmonic ratio (NHR) parameters before and after hormone replacement therapy (HRT) or follow-up in three groups.

or interactions on F0 between groups. In the relevant literature, there are several studies that investigated the effect of HRT on voice by several forms of HRT.[8,9,12,13] But, we could not have any study which investigated the effect of nasal form of HRT on voice. After 1-year follow-up, we obtained that voice quality in patients treated with nasal form of HRT was significantly higher than patients without HRT according to VHI and jitter and shimmer. Besides, both in questionnaire and acoustic analysis, greater voice quality improvement was observed in intranasal estrogen group compared to oral E2 group in acoustic analysis. Nasal spray form of HRT was recently introduced.[22] It is expected that the target estrogen concentration is supplied more rapidly than other forms. If a patient need more stable voice after menopause, intranasal form of estrogen replacement therapy would suggest to the patients instead of other forms. We thought that this novel knowledge of nasal form of HRT could make a contribution to the relevant literature.

Our data demonstrates that voice undergoes changes in lack of estrogen and intranasal form of HRT improves the voice quality more than oral form of it in surgically induced menopausal women. In conclusion, this has led otolaryngologists to prefer intranasal form of HRT when they need to keep their voice stable in patients like voice teachers or voice performers at postmenopausal state.

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