Comparative efficacy of treatments for genitourinary syndrome of menopause

Mekan R. Orazov[1], Viktor E. Radzinskiy[2], Elena S. Silantyeva[3], Liudmila M. Mikhaleva[4], Elizaveta A. Khripach[5], Evgeniy D. Dolgov[6]

[1]D. Sci. (Med.), Prof., Corr. Memb. RAS, People's Friendship University of Russia (RUDN University). E-mail: radzinsky@mail.ru; ORCID: 0000-0003-4956-0466

[2]Peoples' Friendship University of Russia, Moscow, Russian Federation

[3]D. Sci. (Med.), Clinical Hospital "Lapino-1" "Mother and Child", Moscow, Russian Federation. ORCID: 0000-0002-7667-3231

[4]D. Sci. (Med.), Prof., Avtsyn Research Institute of Human Morphology of Petrovsky National Research Centre of Surgery, Moscow, Russian Federation. ORCID: 0000-0003-2052-914X

[5]Obstetrician-Gynecologist, Multidisciplinary Medical Center "DEKA Medical". 16/2 Shmitovsky passage, Moscow, Russian Federation Phone: (499) 938-9528. E-mail: elizaveta.ark@mail.ru. ORCID: 0000-0003-2895-1193

[6]5th year student of the Faculty of Medicine, Student of the Medical Institute, People's Friendship University of Russia. 6, Miklukho-Maclay st, Moscow, Russian Federation. E-mail: 1586dolgde@gmail.com. ORCID: 0000-0001-6709-5209.

SUMMARY (Abstract)

Study Objective: To evaluate the comparative efficacy of the treatments for genitourinary syndrome of menopause.**Study Design:** An open-label, multicentre, prospective, comparative study**Materials and Methods:** This study included 114 patients aged 52.04 ± 1.48 years with a verified diagnosis of postmenopausal atrophic vaginitis (ICD N.95.2) who provided voluntary informed consent to participate in this study. Patients were divided into two study groups. To treat vulvovaginal atrophy, patients in group I (n = 59) administered intravaginal suppositories containing 0.5 mg of estriol, 1 suppository per day for the first 4 weeks and then 1 suppository 2 times a week for 8 weeks. Thus, the total course of topical hormone therapy was 3 months. In group II (n = 55) all patients underwent laser remodeling of the vulvovaginal area using the SmartXide2 V2LR Monalisa Touch laser system (DEKA, Florence, Italy) in the mode of 40/1400/1000/1 ST/DP for 3 sessions in total with a 1-month interval. Thus, the total laser remodeling treatment course was 3 months. The control group (n = 30) included women of similar age who did not have a verified diagnosis of postmenopausal atrophic vaginitis, N95.2.For objectification, the clinical manifestations of GSM in study patients were scored using a 5-point D. Barlow scale and the vaginal health index was calculated (G. Bachmann, 1995).**results:** The mean age of patients in groups I and II was 51.85 ± 1.37 and 52.1 ± 1.26 years with the mean postmenopausal period of 2.44 ± 0.86 years and 2.26 ± 0.84 years, respectively. Thus, the mean time from the onset of clinical manifestations of vulvovaginal atrophy was 2.32 ± 0.84 years in group I and 2.26 ± 0.84 years in group II.In this study, two treatment options, i.e., the topical hormone therapy and the microablative laser remodeling treatment using the SmartXide2 V2LR Monalisa Touch fractional CO2 laser (DEKA, Florence, Italy) in the mode of 40/1400/1000/1 ST/DP, demonstrated similar clinical efficacy in management of GSM symptoms and restoration of vaginal health in studied patients and had no adverse effects associated with burns and/or adhesions to the vaginal mucosa.conclusions: The use of the SmartXide2 V2LR Monalisa Touch fractional CO2 laser (DEKA, Florence, Italy) in treatment of GSM is pathogenetically justified and is an effective treatment option in postmenopausal patients with contraindications to topical hormone therapy.

Key words: vulvovaginal atrophy, genitourinary syndrome of menopause, vaginal dryness, laser treatment, estrogen therapy, topical hormone therapy.

Background

The anti-ageing medicine is one of the most important perspectives of modern gynecology. Genitourinary syndrome of menopause (GSM), which includes the progressive atrophy of genitourinary tissues, is considered to be the "classic" manifestation of age-related hypoestrogenism after neurovegetative symptoms. This nosology can be described as a "pandemic" among postmenopausal women because the prevalence range is truly surprising: from 24% to 84% of all postmenopausal women [1]. GSM is an extremely significant and frequently encountered problem, the full resolution of which warrants the search for new effective therapeutic approaches to management of the symptoms of vulvovaginal atrophy [2].

doi.org/10.31838/hiv23.03.289 Received: 26.11.22, Revised: 24.12.22, Accepted: 23.01.23.

However, it is important to describe GSM in terms of its clinical manifestations. Thus, vulvovaginal atrophy occurs due to impairment of the histoarchitecture and thinning of the epithelial compartment of the vulvovaginal area, both associated with hypestrogenism [3]. Moreover, the insufficient effect of estrogens on the genitourinary tissues translates into the decreased levels of glycogen in the cells of the vaginal mucosa; and since glycogen is a nutrient medium for beneficial lactic acid bacteria, the population of these microorganisms decreases significantly [2,3]. As a consequence, the impaired production of lactic acid by these bacteria causes an inevitable shift to alkaline vaginal pH, decreased colonization resistance and development of infectious diseases. These pathological changes lead to a number of clinical manifestations, such as dyspareunia, dysorgasmia, social disadaptation, dysuria, urinary incontinence, etc. [4]. In view of this it is important to look into the underlying causes of vulvovaginal atrophy, namely, the structure of the pathogenetic cascade of GSM.

As stated previously, menopausal disorders, including GSM, are caused by a natural age-related hypoestrogenism due to the depletion of the ovarian reserve. In this regard, it is necessary to mention the biological effects of estrogens on the female body, the impairment of which leads to a number of pathological conditions in postmenopausal women [4].

Undoubtedly, there are absolute reasonable grounds for the topical estrogen therapy to be pathogenetically justified in any atrophic disorders associated with menopause. It is fair to say that having a significantly lower systemic effect compared to estradiol preparations, topically applied estriol improves the blood supply to the vaginal wall, restores the transudative function of the mucous membrane of the genitourinary tract, maintains sufficient thickness and elasticity of the epithelium and the level of glycogen synthesis in the vaginal fluid, and also stimulates the secretion of immunoglobulins, i.e., it prevents vaginitis [5-7].

Topical hormone therapy with low doses of estrogen is the gold standard treatment for vulvovaginal atrophy [4]. However, estrogen-associated absolute contraindications prompt the search for new approaches to the treatment of GSM with laser remodeling of the vaginal wall being one of these options of great scientific interest in terms of studying its safety and efficacy profile.

Study objective

To evaluate the comparative efficacy of the treatments for genitourinary syndrome of menopause.

Study design

An open-label, multicentre, prospective, comparative study

Materials and methods

190 postmenopausal patients were randomized in this study. 25 patients did not meet the inclusion criteria, 32 non-compliant individuals did not follow the treating physician's recommendations, and 19 subjects withdrew from the study due to a change of residence. This study included a total of 114 patients aged 52.04 ± 1.48 years who were undergoing treatment at the clinical site of the Department of Obstetrics and Gynecology with a course of perinatology of the Peoples' Friendship University of Russia with a verified diagnosis of postmenopausal atrophic vaginitis (ICD N.95.2) and provided their voluntary informed consent for enrollment in this study. The overall cohort was divided into two study groups. To treat vulvovaginal atrophy, patients in group I (n = 59) administered intravaginal suppositories containing 0.5 mg of estriol, 1 suppository per day for the first 4 weeks and then 1 suppository 2 times a week for 8 weeks. Thus, the total course of topical hormone therapy was 3 months. In group II (n = 55) all patients underwent laser remodeling of the vulvovaginal area using the SmartXide2 V2LR Monalisa Touch laser system (DEKA, Florence, Italy) in the mode of 40/1400/1000/1 ST/DP for 3 sessions in total with a 1-month interval. Thus, the total laser remodeling treatment course was 3 months.

The control group (n = 30) included women of similar age who did not have a verified diagnosis of postmenopausal atrophic vaginitis, N95.2.

For objectification, the clinical manifestations of genitourinary syndrome of menopause in studied patients were scored using a 5-point D. Barlow scale. Based on the above signs, vulvovaginal atrophy was objectified by calculating the Vaginal Health Index (G. Bachmann, 1995).

A gynecological exam included an examination of the external and internal genital organs with a detailed examination of the mucous membrane of the vagina and cervix. All patients underwent pH-metry using a color scale.

For statistical analysis, the results were processed using IBM SPSS v.23.0 and StatTech software. The arithmetic means, standard deviations and errors of means were calculated. Statistical significance of differences between values was assessed using non-parametric criteria, i.e., the Mann-Whitney U-test and the Kruskal-Wallis H-test.

To compare the study groups, the t-test was used with a significance level of $p < 0.05$

Results

The mean age of patients in the study cohort (n = 114) was 52.04 ± 1.48 years with the mean age of 51.85 ± 1.37 and 52.1 ± 1.26 years in groups I and II, respectively. There were no statistically significant differences between the study groups and the control group (mean age = 51.17 ± 1.62) (p = 0.212). The mean postmenopausal period was 2.44 ± 0.86 years and 2.26 ± 0.84 years in group I and group II, respectively, with no statistically significant differences in postmenopausal period between the study groups and the control group (p = 0.285). Data on duration of clinical manifestations of GSM were

collected in all patients in the study cohort. The mean time from the onset of clinical manifestations of vulvovaginal atrophy was 2.32 ± 0.84 years in group I and 2.26 ± 0.84 years in group II with no statistically significant differences between the study groups (p = 0.827). Patients' complaints in the study cohort were stratified during the collection of clinical medical history. Thus, vaginal complaints included 3 main domains (irritation, itching, dryness) and were reported in 100% of patients in both study groups with all 3 signs observed in 44.1% and 36.4% of patients in groups I and II, respectively.

In groups I and II, vaginal health scores using the G. Bachmann scale significantly increased 1.27-fold (2.98 ± 0.75 vs. 3.78 ± 1.15; p = 0.006) and 1.17-fold (3.14 ± 0.65 vs. 3.66 ± 1.58; p = 0.006) and 1.06-fold (2.98 ± 0.75 vs. 3.17 ± 0.79; p = 0.013) and 1.0032-fold (3.14 ± 0.65 vs. 3.15 ± 1.04; p = 0.013), respectively, 3 and 6 months after the GSM treatment. Meanwhile, the rate of clinical manifestations of GSM (based on the analysis of the complaint rate in the study cohort) significantly decreased 1.84-fold (2.95 ± 1.24 vs. 1.6 ± 1.04; p < 0.001) and 2.15-fold (2.93 ± 1.14 vs. 1.36 ± 0.91; p < 0.001) and 1.48-fold (2.95 ± 1.24 vs. 2 ± 0.8; p < 0.001) and 1.97-fold (2.93 ± 1.14 vs. 1.49 ± 0.96; p < 0.001) in groups I and II, respectively, 3 and 6 months after the treatment of vulvovaginal atrophy. The study revealed significant differences in D.Barlow scores of the study groups and the control group both at baseline (2.95 ± 1.24 and 2.93 ± 1.14 vs. 0.07 ± 0.25; p < 0.001) and 3 months (1.6 ± 1.04 and 1.36 ± 0.91 vs. 0.07 ± 0.25; p<0.001) and 6 months (2 ± 0.8 and 1.49 ± 0.96 vs. 0.07 ± 0.25; p < 0.001) after the treatment.

Therefore, in this study two treatment options, i.e., the topical hormone therapy using intravaginal suppositories containing 0.5 mg of estriol and the microablative laser remodeling treatment using the SmartXide2 V2LR Monalisa Touch fractional CO2 laser (DEKA, Florence, Italy) in the mode of 40/1400/1000/1 ST/DP, demonstrated similar clinical efficacy in management of GSM symptoms and restoration of vaginal health in studied patients and had no adverse effects associated with burns and/or adhesions to the vaginal mucosa.

Discussion

Vaginal atrophy is one of the most common pathological conditions in peri- and postmenopausal women and is characterized by manifestations which negatively impact the quality of life of the affected individuals [5,6,7,8]. Changes in the genitourinary tract associated with the end of the reproductive period of life and with the inevitable aging represent one of the most urgent problems of modern gynecology [9]. To describe estrogen-dependent age-related changes affecting the vulva, vagina, urethra and bladder, a new term was adopted, i.e., a genitourinary syndrome of menopause, GSM (IMS, 2014) [9]. As it follows from the above, the use of topical hormone therapy to treat GSM is absolutely pathogenetically justified, and the topical estriol preparations demonstrate high efficacy and safety. However, it is worth noting that the gold standard treatment for GSM also has the disadvantage that within 1–3 months after discontinuation of topical estrogens one should expect the recurrence of de novo symptoms [10]. Undoubtedly, this not only merits the attention of the global gynecological community, but also sets forth a search trajectory for new therapeutic approaches that can "reverse" the progressive symptoms of vulvovaginal atrophy and "block" GSM at the level of its pathogenetic patterns [11].

It is important to mention the findings of a large meta-analysis by Filippini M. et al. (2022), who studied the effects of laser remodeling treatment on the clinical manifestations of GSM. There was a clear decreasing trend observed in the clinical symptoms of all major subjective patterns of vulvovaginal atrophy: dryness -5.15 (95% CI: -5.72, -4.58; p < 0.001; I2: 62%; n = 296), dyspareunia -5.27 (95% CI: -5.93, -4.62; p < 0.001; n = 296), itching -2.75 (95% CI: -4.0, -1.51; p < 0.001; I2: 93%; n = 281), burning sensation -2.66 (95% CI: -3.75, -1.57; p < 0.001; n = 296) and dysuria -2.14 (95% CI: -3.41, -0.87; p < 0.001; n = 281). In addition, there was a pronounced increase in the female sexuality index, which showed a mean difference of 10.8 (95% CI: 8.41,13.37; p < 0.001; n = 273) [12].

The findings of a recent meta-analysis by Mension E. et al. (2021), which included 64 studies, are also worth mentioning. Vulvovaginal laser remodeling was found to lead to a number of improvements. Thus, there was a pronounced decrease in the visual analog scale score due to the relief of dyspareunia, an increase in the female sexuality index due to the treatment of signs of sexual dysfunction, as well as an increase in the vaginal health index which objectifies the results obtained [13].

In this regard, it is important to mention an extremely promising, although not reflected in the world clinical guidelines, treatment option for GSM, namely, the laser remodeling of the vulvovaginal area. Despite the fact that the use of laser technologies in gynecological practice is quite a novelty, the laser tissue remodeling has been used in cosmetology for a long time. Currently, the fractional microablative CO_2 laser is one of the most technically advanced and state-of-art devices. Based on the above, it is important to note that the use of fractional CO_2 laser in patients with verified GSM demonstrated high efficacy and safety with no adverse effects.

In summary, we have looked into the new understandings of the mechanisms of pathogenesis and the main therapeutic approaches to the treatment of vulvovaginal atrophy, both "classic" and innovative and extremely promising. In light of the fact that topical hormone therapy and a course of laser remodeling procedures demonstrated similar efficacy in relieving symptoms of GSM, laser remodeling of the vulvovaginal area can be used as the first-line treatment in patients with contraindications to topical estrogen therapy or hormonophobia.

Conclusions

In this study, two treatment options, i.e., the topical hormone therapy and the microablative laser remodeling treatment using the SmartXide2 V2LR Monalisa Touch fractional CO2 laser (DEKA, Florence, Italy) in the mode of 40/1400/1000/1 ST/DP, demonstrated similar clinical efficacy in management of GSM symptoms and restoration of vaginal health in studied patients and had no adverse effects associated with burns and/or adhesions to the vaginal mucosa.

The use of the SmartXide2 V2LR Monalisa Touch fractional CO2 laser (DEKA, Florence, Italy) in treatment of GSM is pathogenetically justified and is an effective treatment option in postmenopausal patients with contraindications to topical hormone therapy.

Disclosure of interest

The authors declare that they have no competing interests.

Authors' contribution

The authors declare the compliance of their authorship according to the international ICMJE criteria.

All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Funding source

The authors declare that there is no external funding for the exploration and analysis work.

References

1. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020 Sep;27(9):976-992. doi: 10.1097/GME.0000000000001609. PMID: 32852449.

2. Parish SJ, Nappi RE, Krychman ML, Kellogg-Spadt S, Simon JA, Goldstein JA, Kingsberg SA. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. Int J Womens Health. 2013 Jul 29;5:437-47. doi: 10.2147/IJWH.S44579. PMID: 23935388; PMCID: PMC3735281.

3. Ventura-Clapier, R., Piquereau, J., Veksler, V., & Garnier, A. (2019). Estrogens, estrogen receptors effects on cardiac and skeletal muscle mitochondria. *Frontiers in endocrinology*, *10*, 557.

4. Peters, Kelly Jo. "What Is Genitourinary Syndrome of Menopause and Why Should We Care?." *The Permanente journal* vol. 25 (2021): 20.248. doi:10.7812/TPP/20.248

5. Mueck AO, Ruan X, Prasauskas V, et al. Treatment of vaginal atrophy with estriol and lactobacilli combination: a clinical review. Climacteric. 2018;21(2):140-7

6. Xiang, D., Liu, Y., Zhou, S., Zhou, E., & Wang, Y. (2021). Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxidative Medicine and Cellular Longevity*, *2021*.

7. Maseroli E. et al. Anti-inflammatory effects of androgens in the human vagina //Journal of Molecular Endocrinology. – 2020. – Vol. 65. – No. 3. – pp. 109-124.

8. Orazov M.R., Demyashkin G.A., Toktar L.R. Remodeling laser therapy of the vagina in genitourinary menopausal syndrome //Surgical practice. – 2018. – No. 1. – pp. 22-37.

9. Tadir Y. et al. Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies //Lasers in surgery and medicine. – 2017. – Vol. 49. – No. 2. – pp. 137-159.

10. Peach C. J. et al. Molecular pharmacology of VEGF-A isoforms: binding and signalling at VEGFR2 //International journal of molecular sciences. – 2018. – Vol. 19. – No. 4. – P. 1264.

11. Marelli-Berg, F. M., Clement, M., Mauro, C., & Caligiuri, G. (2013). An immunologist's guide to CD31 function in T-cells. *Journal of cell science*, *126*(11), 2343-2352.

12. Filippini, M., Porcari, I., Ruffolo, A.F., Casiraghi, A., Farinelli, M., Uccella, S., Franchi, M., Candiani, M. and Salvatore, S., 2022. CO2-Laser therapy and Genitourinary Syndrome of Menopause: A Systematic Review and Meta-Analysis. *The Journal of Sexual Medicine*.

13. Mension, E., Alonso, I., Tortajada, M., Matas, I., Gómez, S., Ribera, L., Anglès, S. and Castelo-Branco, C., 2021. Vaginal laser therapy for genitourinary syndrome of menopause–systematic review. Maturitas.