ISSN: 2977-0033

Research Article

Journal of Clinical Research and Case Studies

Transdermal Carboxytherapy for Treating Vulvovaginal Atrophy: A Pilot Study

Kimberly Evans[1], Gustavo H Leibaschoff[2*] and Red M Alinsod[3]

[1]MD Sugar Land Medical Spa Sugar Land, TX, USA
[2]MD World Society of Cosmetic Gynecology Dallas, TX , USA
[3]MD Alinsod Institute Dallas Dallas, TX , USA

[*]Corresponding author
Gustavo H Leibaschoff, International Consultants in Aesthetic Medicine 3225 Turtle Creek Boulevard Dallas, TX 75219, USA.

Received: September 05, 2024; **Accepted:** September 12, 2024; **Published:** September 16, 2024

ABSTRACT

Objective: Genitourinary syndrome of menopause (GSM) is a prevalent disorder that can negatively impact the overall health, sexual function, and quality of life of affected women; however, available data do not support specific treatment protocols. A novel product enables the noninvasive transdermal administration of carboxytherapy with a topical gel (CO_2Lift®, Lumisque, Inc.; Weston, FL). The following randomized, placebo-controlled pilot study assessed the safety and efficacy of the transdermal carboxytherapy gel for treating GSM-related vulvovaginal changes. Methods: Menopausal or postmenopausal women 40 to 70 years old with signs or symptoms of vulvovaginal atrophy and Female Sexual Dysfunction were randomized to receive topical carboxytherapy gel (n=40) or placebo gel (n=10) in a randomized, double-blind fashion. The assigned treatments were placed into the vagina and on the vulva for 45 minutes before removal. Treatment was applied daily for 5 days, stopped for 2 days, then continued for 5 additional days. Subjects completed four validated pre- and posttreatment questionnaires to assess female sexual function, sexual health, and genital self-image. Additionally, control (n=10) and treatment subjects (n=10) were randomized to undergo 3 mm pre- and posttreatment punch biopsies of vulva and vaginal tissue.

Results: Overall, carboxytherapy-treated subjects achieved significant improvements in Female Sexual Function Index scores with strong positive correlations between sexual desire and arousal, arousal and sexual satisfaction, and sexual satisfaction and desire. The Day-to-Day Impact of Vaginal Aging Questionnaire results demonstrated a significant difference in mean pre- and posttreatment values for each assessment among subjects receiving topical carboxytherapy. Biopsy improvements included hyperplasia of the keratinized squamous epithelium, discrete hyperplasia of the basal layer and neovascularization, and increased thickness of mucous squamous epithelium. There were no adverse events.

Conclusion: Transdermal carboxytherapy represents a safe, noninvasive means of treating the genitourinary syndrome of menopause symptoms and is suitable for home use. Additional research on this treatment is warranted.

Keywords: Bohr effect, Genitourinary syndrome of menopause, Histology, Pilot study, Transdermal carboxytherapy gel, Vulvovaginal atrophy

Introduction

Genitourinary syndrome of menopause (GSM) refers to the signs and symptoms caused by decreased estrogenic stimulation of the vulvovaginal and lower urinary tracts [1]. GSM can have a severe negative impact on the overall health, sexual function, and quality of life of affected women [1]. The North American Menopause Society estimates that 27 to 84% of postmenopausal women are affected by GSM [2]. Unfortunately, GSM appears to be an underdiagnosed and undertreated condition. Currently, available treatments include, but are not limited to, vaginal lubricants and moisturizers, vaginal estrogens and dehydroepiandrosterone, and systemic hormone therapy, such as ospemifene; However, insufficient data is available at this time for specific treatment recommendations [2,3].

There has been growing interest in carboxytherapy within several fields of medicine. Carboxytherapy refers to the injection of carbon dioxide gas (CO_2) into tissue, which owes its therapeutic benefit to the so-called Bohr effect, first described by the Danish physiologist Christian Bohr [4]. In response to an increase in tissue CO_2 and decreased pH, the oxygenhemoglobin dissociation curve shifts rightward, favoring the release of oxygen (O_2) from the blood into local tissue.

Citation: Kimberly Evans, Gustavo H Leibaschoff, Red M Alinsod. Transdermal Carboxytherapy for Treating Vulvovaginal Atrophy: A Pilot Study. J Clin Res Case Stud. 2024. 2(3): 1-8. DOI: doi.org/10.61440/JCRCS.2024.v2.52

Recently, a novel product has been developed that enables the noninvasive transdermal administration of carboxytherapy with a topical gel (CO_2Lift®, Lumisque, Inc.; Weston, FL). Once activated and applied to the skin, the product releases CO_2, which is absorbed into the skin, where the Bohr effect produces its therapeutic benefits [5,6]. To date, no adverse events have been associated with topical carboxytherapy gel.

A small pilot study previously assessed the effects of this transdermal carboxytherapy gel for vulvovaginal regeneration in postmenopausal women experiencing symptoms of GSM [7]. Women with moderate-to-severe signs or symptoms of vulvovaginal atrophy were randomized to receive treatment with transdermal carboxytherapy (n=10) or a placebo (ultrasound gel, n=10). Subjects applied their assigned treatments to the vulvovaginal area daily at home for 5 days, followed by a 2-day break, then daily again for 5 additional days. Subjects who received carboxytherapy achieved significant improvements on the Female Sexual Function Index (FSFI) and Day-to-Day Impact of Vaginal Aging (DIVA) Questionnaires. Biopsy samples obtained from the vagina and vulva revealed a regenerative effect on vulvovaginal tissues. Placebo-treated subjects received no benefits from their treatment.

Based on these positive results, a larger randomized, placebocontrolled pilot study was performed to further assess the safety and efficacy of the transdermal carboxytherapy gel for treating GSM-related vulvovaginal changes.

Methods

Study Subjects

Enrolled subjects were menopausal or postmenopausal women (N=50) 40 to 70 years old with signs or symptoms of vulvovaginal atrophy and Female Sexual Dysfunction (FSD) [8]. Each subject expressed her willingness to adhere to all study requirements. Subjects were randomized to receive topical carboxytherapy gel intervention (n=40) or placebo gel (n=10) in a randomized, double-blind fashion. If the carboxytherapy treatment provided beneficial effects, the placebo group would also later receive carboxytherapy treatment.

Reasons for exclusion from study participation included asymptomatic vulvovaginal atrophy; genital allergy, eczema, disease, or inflammation; sexual inactivity; change in hormone therapy during the previous 3 months; antibiotic therapy in the last 2 months; current tamoxifen therapy; a history of vulvar disease or cancer; use of a vaginal pessary; or body mass index (BMI) >30 kg/m^2.

Table 1: Female Sexual Function Index: Correlation Analysis

	Arousal	Desire	Lubrication	Orgasm	Pain
Desire	0.435	--	--	--	--
Lubrication	-0.020	0.107	--	--	--
Orgasm	-0.096	-0.078	-0.026	--	--
Pain	-0.462	-0.090	0.026	-0.008	--
Satisfaction	0.658	0.341	-0.250	-0.043	-0.417

Study Treatment

The study treatment was a proprietary topical carboxytherapy gel designed as a take-home vaginal rejuvenation treatment (CO_2Lift® V, Lumisque, Inc.; Weston, FL). A similar-appearing product containing an inert gel was provided as a placebo. Within the active and placebo treatment kits were cards, further blindly randomizing subjects into biopsy groups.

Subjects were instructed on how to mix the two product components to activate it. Using a provided applicator, a specified quantity of gel was to be inserted into the vagina (~2/3) and placed on the vulva (~1/3). The gel was left in place for at least 45 minutes but could be left longer. The gel was rinsed out of the vagina with water using the applicator and washed off the vulva. Subjects were to apply the treatment daily for 5 days, stop for 2 days, then continue treatment for 5 additional days. Detailed written directions on how and when to use the product were provided, and follow-up phone calls were made during the study to support the correct use of the product.

Study Assessments

Each subject completed standardized pre- and post-treatment questionnaires comprised of four instruments validated for use as selfreported scales for female sexual function, sexual health, and genital selfimage. The questionnaires were administered at baseline and after the 2week treatment period:

- The Female Sexual Function Index (FSFI) is a validated 19-item scale that includes the following six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI detects sexual dysfunction and can lead to therapeutic indications [9].
- The Day-to-Day Impact of Vaginal Aging Questionnaire (DIVA) measures the quality of life by considering daily activities, emotional well-being, sexual functioning, and self-concept/body image (Table 1). It evaluates the impact of vaginal dryness, soreness, itching, irritation, and pain on the sexual function and well-being of postmenopausal women [10].
- The King's Health Questionnaire measures the impact of urinary incontinence on sexual health and genital self-image [11]. Severity
- Measures were responses to the questions: "A, wear pads to keep dry?", "B, be careful about how much fluid you drink?" "C, change your underclothes because they get wet?" "D, worry in case you smell?" Possible responses were 1, Never; 2, Sometimes; 3, Often; 4, All the time.
- The Female Genital Self-Image Scale (FGSIS) is a validated 7-item measure to evaluate genital self-image and understand implications for sexual health and sexual and gynecological health behaviour [12].

Table 2: Day-to-Day Impact of Vaginal Aging Questionnaire

For Questions 1 to 18, respond by indicating 0, Not at all; 1, A little bit; 2, Moderately; 3, Quite a bit; 4, Extremely. For Questions 12 to 15, you may choose Not applicable, I have not had sexual activity of any kind recently. For Questions 19 to 22, respond by indicating 0, Not at all true; 1, A little true; 2, Somewhat true; 3, Mostly true; 4, Definitely true.
Part A. During the past 4 weeks, how much have vaginal symptoms such as dryness, soreness, irritation, or itching made it uncomfortable or interfered with your ability to:
1. Walk at your usual speed?
2. Wear the clothing or underwear you want?
3. Use the toilet or wipe yourself after using the toilet?
4. Sit for more than an hour?
5. Get a good night's sleep?
Part B. During the past 4 weeks, how often have vaginal symptoms such as dryness, soreness, irritation, or itching caused you to feel:
6. Depressed or down?
7. Embarrassed?
8. Frustrated or resentful?
9. Bad about yourself?
Part C. The following questions ask about the impact of your symptoms on vaginal sexual intercourse as well as other types of sexual activity such as self-stimulation or masturbation. During the past 4 weeks, have vaginal symptoms such as dryness, soreness, irritation, or itching affected:
10. Your desire or interest in having sexual intercourse or other types of sexual activity (including self-stimulation or masturbation)?
11. How frequently you had sexual intercourse or other types of sexual activity (including self-stimulation or masturbation)?
12. Your ability to become aroused during sexual activity (including selfstimulation or masturbation)?
13. Your ability to be spontaneous about sexual activity (including selfstimulation and masturbation)?
15. The amount of pleasure you experienced during sexual activity (including self-stimulation or masturbation)?
16. Your desire or interest in being in a sexual relationship?
17. Your confidence that you could sexually satisfy a partner?
18. Your overall satisfaction with your sex life?
Part D. The following statements describe ways in which your vaginal symptoms may have affected your feelings about yourself and your body. Please indicate how true each of the following statements has been for you during the past 4 weeks.
19. My vaginal symptoms make me feel like I'm getting old.
20. I feel undesirable because of my vaginal symptoms.
21. When I think about my vaginal symptoms, I feel like I have lost something.
22. My vaginal symptoms make me feel like my body is deteriorating.
22. I feel less sexy because of my vaginal symptoms.

From: Huang, et al. Day-to-Day Impact of Vaginal Aging questionnaire: A multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. Menopause. 2015. 22: 144.

Tissue Biopsies

Ten control and ten treatment subjects were randomly selected to undergo 3 mm pre- and posttreatment punch biopsies. Tissue samples were obtained from the vulva labia majora and the left vaginal lateral wall of the outer vagina. The biopsies were sent to an independent laboratory for preparation and hematoxylin and eosin staining. A qualified pathologist evaluated biopsy preparations.

Study Endpoints

The study efficacy endpoints were the posttreatment vulvovaginal changes as assessed by the DIVA Questionnaire, FSFI Scale, King's Health Questionnaire, and FGSIS Scale scores versus placebo treatment and changes in posttreatment biopsy samples versus placebo treatment.

Safety endpoints were reported adverse events (AEs) in subjects receiving active treatment versus placebo treatment. AEs of particular importance were skin irritation, allergy to the product, changes in local circulation, local redness or swelling, changes in vaginal moisture, and change in sensitivity during intercourse.

Statistical Analysis

Paired t-tests were used to detect pre- and posttreatment differences in each dimension of the Female Sexual Function Index, Day-to-day Impact of Vaginal Aging, King´s Health Questionnaire, and Female Genital Self-Image Questionnaire. A correlation analysis using Pearson's coefficient was applied to investigate the linear relationship between the differences in pre- and posttreatment values for each dimension of the Female

Sexual Function Index and King´s Health Questionnaire. A significant difference was established at p≤0.05.

Ethics

The study protocol and related materials were approved by a commercial IRB (Allendale Investigational Review Board, Old Lyme, CT). Each subject provided written informed consent before participating in any study-related activities. The conduct of this study followed all applicable guidelines for the protection of human subjects for research as outlined in United States FDA 21 CFR Part 50, And under the accepted standards for good clinical Practices [13,14].

Results

Female Sexual Function Index

Analysis of pre- and posttreatment values for mean FSFI items revealed significant changes for Desire (p=0.000), Arousal (p=0.000), satisfaction (p=0.000), Pain (p=0.000), Lubrication (p=0.001) and Orgasm (p=0.036) (Figure 1). The mean pre- and posttreatment values for placebocontrolled subjects did not achieve statistical significance, although fewer subjects did.

The results of a correlation analysis between questionnaire items revealed moderate positive correlations suggesting significant relationships between sexual desire and arousal (0.435), arousal and sexual satisfaction (0.658), and sexual satisfaction and desire (0.341). In contrast, there were moderate negative correlations between pain and sexual arousal (-0.462), pain and sexual satisfaction (-0.417), and lubrication and sexual satisfaction (-0.250).

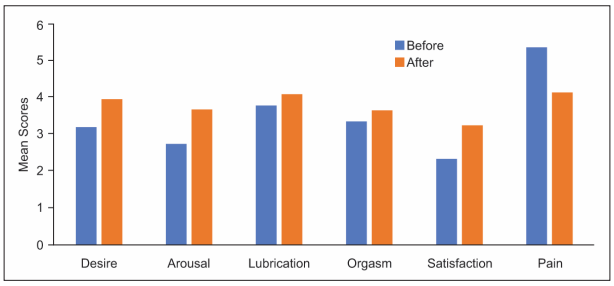

Figure 1: Female Sexual Function Index

Analysis of the change in pre- and posttreatment values were significant for Desire (p<0.000), Arousal (p<0.000), Satisfaction (p<0.000), Pain (p<0.000), Lubrication (p=0.001) and Orgasm (p=0.036).

Day-to-Day Impact of Vaginal Aging

The paired t-test results indicate a significant difference in mean pre- and posttreatment values for each assessment (for each, p<0.05) (Figure 2). There were no significant differences in mean pre- and posttreatment values for placebo-treated subjects.

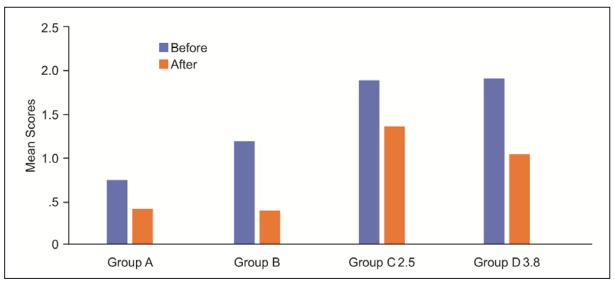

Figure 2: Day-to-Day Impact of Vaginal Aging

The paired t-tests results indicate a significant difference in mean pre- and posttreatment values for each assessment (for each, p<0.05).

King´s Health Questionnaire

For most questionnaire items, there was a significant difference between mean pre- and posttreatment values (p=0.000) except Health (p=0.205), and Severity (p=0.146) (Figure 3).

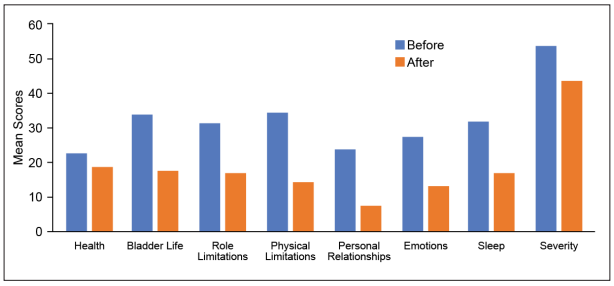

Figure 3: King´s Health Questionnaire

For most questionnaire items, there was a significant difference between mean pre- and posttreatment values (p<0.000) except Health (p=0.205), and Severity (p=0.146).

There was no significant difference between mean pre- and posttreatment values for placebo-treated subjects. The correlation analysis revealed the following relationships:

- Strong, positive correlations between Incontinence Severity and Role Limitations (0.676) and severity and Physical Limitations (0.578). And Severity and Emotions (0.593).
- Moderate, positive correlations between Role Limitations and Bladder Life (0.607), Physical Limitations and Role Limitations (0.598), Physical Limitations and Bladder Life (0.570), Personal Relationships and Role Limitations (0.508), Personal Relationships and Physical Limitations (0.405), Emotions and Bladder Life (0.654), Emotions and Role Limitations (0.539), Emotions and Physical Limitations (0.552), Emotions and Personal Relationships (0.524), Sleep and Bladder Life (0.456), Sleep and Role Limitations (0.512), Sleep and Physical Limitations (0.475), Sleep and Personal Relationships (0.601), Sleep and Emotions (0.487), Severity and Personal Relationships (0.509), and Severity and Sleep (0.554), and Severity and Bladder Life (0.612).
- Weak positive correlation between Personal relationships and Bladder Life (0.335).
- No or negligible correlation between Severity and Health (-0.008).
- Moderate negative correlation between Emotions and Health (-0.298).
- Weak negative correlations between Bladder life and Health (-0.119), Role limitations and Health (-0.051), Physical limitations and Health (-0.128), Personal Relationships and Health (-0.128), and Sleep and Health (-0.048).

Female Genital Self-Image

Mean pre- and posttreatment Self-Image Scale scores significantly increased for carboxytherapy-treated subjects (p=0.000) and those treated with placebo gel (p=0.012).

Tissue Biopsies

Carboxytherapy-Treated Vulva. Before treatment with carboxytherapy, keratinized squamous epithelium was observed in one patient in the vulva with areas of thinning and loss of ridge networks (Figure 4). Chorion, which consists of dense connective tissue with mild chronic inflammation and congestion, was observed. Following treatment, hyperplasia of the keratinized squamous epithelium with discrete basal layer hyperplasia was seen. The chorion comprised dense connective tissue with mild chronic inflammatory lymphocyte infiltrate. The presence of neovascularization was observed.

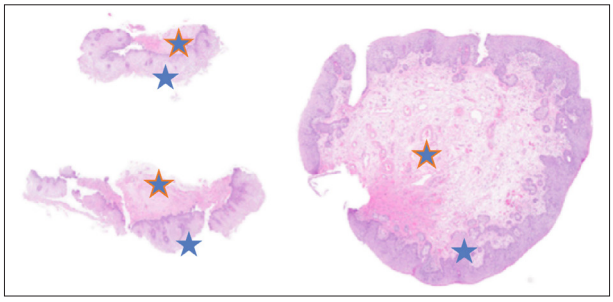

Figure 4: Changes in Vulva Tissue - Carboxytherapy

(Left) Prior to treatment with carboxytherapy, keratinized squamous epithelium was observed in this patient in the vulva with areas of thinning and loss of ridge networks (star). Chorion consisting of dense connective tissue with mild chronic inflammation (orange border star) and congestion was observed. (Right) Following treatment, hyperplasia of the keratinized squamous epithelium with discrete hyperplasia of the basal layer was seen (star). The chorion was made up of dense connective tissue with mild chronic inflammatory lymphocyte infiltrate (orange border star). The presence of neovascularization was observed.

Carboxytherapy-Treated Vagina. In the pre-treatment vaginal tissue, mucous squamous epithelium with glycogenic acanthosis was observed

(Figure 5). After treatment, there was a slight increase in the thickness of the mucous squamous epithelium. The chorion showed increased neovascularization and young fibroblasts.

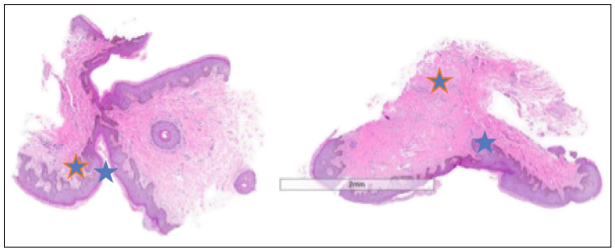

Figure 5: Changes in Vagina Tissue - Carboxytherapy

(Left) In pre-treatment vaginal tissue, mucous squamous epithelium with glycogenic acanthosis was observed (star). (Right) After treatment, there was a slight increase in the thickness of the mucous squamous epithelium.

The chorion (star) showed increased neovascularization and young fibroblasts (orange border star).

Placebo-Treated Vulva. In this patient, the pretreated vulva showed keratinized squamous epithelium with discrete basal layer hyperplasia (Figure 6). The chorion consisted of dense connective tissue with mild chronic inflammation and congestion. Following treatment, the vulva showed no significant changes. It was a keratinized squamous epithelium with discrete hyperplasia of the basal layer. The chorion is comprised of dense connective tissue with mild chronic inflammatory lymphocytes that infiltrate with edema and congestion.

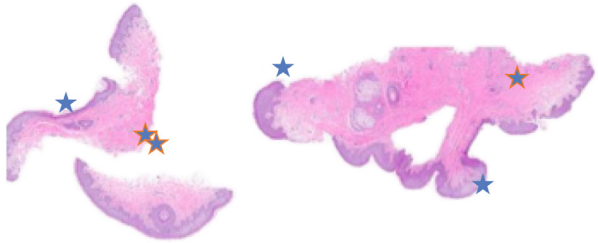

Figure 6: Changes in Vulva Tissue - Placebo

(Left) In this patient, the pretreatment vulva showed keratinized squamous epithelium with discrete hyperplasia of the basal layer (star). The chorion consisted of dense connective tissue with mild chronic inflammation (orange border star) and congestion. (Right) Following treatment, the vulva showed no significant changes. It was a keratinized squamous epithelium with discrete hyperplasia of the basal layer (star). The chorion was made up of dense connective tissue with mild chronic inflammatory lymphocyte infiltrate (orange border star) with edema and congestion.

Placebo-Treated Vagina. The pre-treatment vaginal tissue showed the presence of mucosal squamous epithelium with glycogenic acanthosis and the chorion of vascularized dense connective tissue (Figure 7). Following treatment, there was a slight increase in the thickness of the mucous squamous epithelium. Discrete vascularization was observed in the chorion.

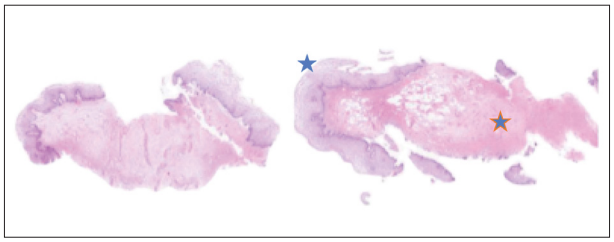

Figure 7: Changes in Vagina Tissue – Placebo

(Left) The pre-treatment vaginal tissue showed the presence of mucosal squamous epithelium with glycogenic acanthosis and the chorion of vascularized dense connective tissue. (Right) Following treatment here was a slight increase in the thickness of the mucous squamous epithelium. Discrete vascularization was observed in the chorion.

Safety

No subject-reported AEs were associated with the application of carboxytherapy or placebo gel.

Discussion

Genitourinary syndrome of menopause (GSM) is a progressive condition caused by diminished estrogens in perimenopausal

and menopausal women [15]. Before 2014, GSM was referred to as vulvovaginal atrophy; however, it now covers a wide range of signs and symptoms associated with decreased estrogen, including changes to the labia majora and minor, clitoris, vestibule, and introitus, vagina, urethra, and bladder [16]. The syndrome may also include symptoms of genital dryness, burning, irritation, lack of lubrication, sexual discomfort or pain, and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections [16,17]. GSM also affects many women undergoing cancer treatment [18,19]. While GSM affects a large population segment, many affected individuals do not seek treatment. Consequently, GSM remains underdiagnosed and undertreated [2].

Treatment options for GSM are limited and provide only temporary relief [20]. Common treatments include lubricants, moisturizers, and estrogencontaining vaginal creams, tablets, and suppositories [21]. Among selective estrogen receptor modulators, only ospemifene is indicated for treating GSM related dyspareunia [22]. Vulvovaginal energy-based devices, including lasers and radio-frequency devices, are under investigation as treatments for GSM, but none have FDA approval for this indication. In 2018, FDA issued a public warning about the use of these devices for vaginal cosmetic purposes, stating that the effectiveness and safety of the devices have not yet been established [23].

Based on the Bohr effect, CO_2 injections can stimulate an acute inflammatory response with peripheral vasodilatation, increased cutaneous microcirculation, Enhanced tissue perfusion and improved oxygenation [24,25]. Consequently, injections of CO_2 gas have been used to improve wound healing in the presence of venous insufficiency, reduce scar formation, treat cellulite and numerous other applications in dermatology and aesthetic medicine [26-34]. The randomized, placebo-controlled study reported here aimed to further assess the safety and efficacy of a novel transdermal carboxytherapy gel for treating vulvovaginal changes associated with GSM in menopausal or postmenopausal women.

Overall, carboxytherapy-treated subjects achieved significant improvements in FSFI scores with strong positive correlations between sexual desire and arousal, arousal and sexual satisfaction, and sexual satisfaction and desire. Not surprisingly, there were negative correlations between pain and sexual arousal, pain and sexual satisfaction, and lubrication and sexual satisfaction.

The Day-to-Day Impact of Vaginal Aging Questionnaire includes four multi-item scales that address symptom impact on activities of daily living, emotional well-being, sexual functioning, and self-concept and body image [10]. The study results demonstrated a significant difference in mean pre- and posttreatment values for each assessment among subjects receiving topical carboxytherapy but no significant differences among placebo-treated subjects.

Most items in the King´s Health Questionnaire showed a significant difference between mean pre- and posttreatment values except for Health and Severity, but no significant pre- and posttreatment differences among placebo-treated subjects. The relationships discovered in the correlation analysis were solid and positive associations between Severity and Role Limitations, Severity and Physical Limitations, and Severity and Emotions. Interestingly, there was a significant increase in mean pre- and posttreatment Femaile Gentital Self-Image Scale scores for both carboxytherapy- and placebo-treated subjects.

Tissue biopsy results revealed several improvements following carboxytherapy, including hyperplasia of the keratinized squamous epithelium with discrete hyperplasia of the basal layer and neovascularization, a slight increase in the thickness of the mucous squamous epithelium. This is a significant key event as vascularization is the foundation for increased vaginal moisture via transudate formation, leading to comfort with sex, lowering of the vaginal pH, and reducing the risk of vaginitis and urinary tract infections. Several topical treatments attribute their beneficial effects to increased vaginal vascularization and restoration of atrophic vaginal tissue [35,36,37].

As the treatment ended after only 10 days of topical carboxytherapy application, it is possible that continued improvements in vaginal tissue would occur with continued treatment. Similar to previous studies with this topical carboxytherapy product, there was no evidence of any physician- or subjectreported adverse events related to the active treatment.

Conclusion

Transdermal carboxytherapy represents a safe, noninvasive means of treating the genitourinary syndrome of menopause and is suitable for home use. Continued application of transdermal carboxytherapy may provide additional benefits for treating the vaginal changes associated with genitourinary syndrome of menopause. Further research on this treatment is warranted.

Acknowledgments

The authors acknowledge the editorial assistance of Dr. Carl S. Hornfeldt, Apothekon, Inc., during the preparation of this manuscript. This study was sponsored by Lumisque, Inc., Weston FL.

Financial Disclosures: Grants, honorarium, speaker's bureau, etc.
Dr. Evans reports nothing to disclose.
Dr. Leibaschoff reports nothing to disclose.
Dr. Alinsod reports nothing to disclose.

Source of Funding: None

References

1. Sarmento ACA, Costa APF, Vieira-Baptista P, Giraldo PC, Eleutério J, et al. Genitourinary syndrome of menopause: Epidemiology, physiopathology, clinical manifestation and diagnostic. Front Reprod Health. 2021. 3: 779398.
2. NAMS 2020 GSM Position Statement Editorial Panel. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020. 27: 976-992.
3. Archer DF, Simon JA, Portman DJ, Goldstein SR, Goldstein I. Ospemifene for the treatment of menopausal vaginal dryness, a symptom of the genitourinary syndrome of menopause. Expert Rev Endocrinol Metab. 2019. 14: 301-314.
4. Bohr C, Hasselbalch K, Krogh A. Concerning a biologically important relationship - the influence of the carbon dioxide content of blood on its oxygen binding. Skand Arch Physiol. 1904. 16: 401-412.

5. Medrano K, Arruda S ON, NS. Carboxytherapy mask as post nanofractional radiofrequency treatment for improvement of facial skin quality and photoaging. J Drugs Dermatol. 2021. 20: 461-465.
6. Draelos ZD, Shamban A. A pilot study evaluating the anti-aging benefits of a CO2-emitting facial mask. J Cosmet Dermatol. 2023. 22: 2198-2204.
7. Leibaschoff GH, Arrieta CTN, Reyes CLG, Melamed JL. A pilot randomized, double-blind, placebo-controlled clinical trial on the efficacy and safety of a transdermal gel that delivers CO2 in the treatment of vulvovaginal atrophy. Surg Technol Int. 2021. 38: 234-239.
8. Khorsandi D, Palacios S, Losa F. Improving women's sexual experience: Efficacy, tolerability and acceptability evaluation of a new nonhormonal intimate gel (Libicare® Gel Íntimo). EC Gynaecology. 2019. 8: 198204.
9. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005. 31: 1-20.
10. Huang AJ, Gregorich SE, Kuppermann M. Day-to-Day Impact of Vaginal Aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. Menopause. 2015. 22: 144-154.
11. Luz R, Pereira I, Henriques A, Ribeirinho AL, Valentim-Lourenço A. King's Health Questionnaire to assess subjective outcomes after surgical treatment for urinary incontinence: Can it be useful. Int Urogynecol J. 2017. 28: 139-145.
12. Herbenick D, Reece M. Development and validation of the female genital self-image scale. J Sex Med. 2010. 7: 1822-1830.
13. United States Food and Drug Administration. Code of Federal Regulations Title. Accessed. 2024.
14. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice. 2024.
15. Wasnik VB, Acharya N, Mohammad S. Genitourinary syndrome of menopause: A narrative review focusing on its effects on the sexual health and quality of life of women. Cureus. 2023. 15: e48143.
16. Portman DJ, Gass ML. Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause. 2014. 21: 1063-1068.
17. Gandhi J, Chen A, Dagur G. Genitourinary syndrome of menopause: An overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. Am J Obstet Gynecol. 2016. 215: 704-711.
18. Cox P, Panay N. Vulvovaginal atrophy in women after cancer. Climacteric. 2019. 22: 565-571.
19. Falk SJ, Bober S. Vaginal health during breast cancer treatment. Curr Oncol Rep. 2016. 18: 32.
20. Benini V, Ruffolo AF, Casiraghi A. New innovations for the treatment of vulvovaginal atrophy: An up-to-date review. Medicina (Kaunas). 2022. 58: 770.
21. Shim S, Park KM, Chung YJ, Kim MR. Updates on therapeutic alternatives for genitourinary syndrome of menopause: Hormonal and nonhormonal managements. J Menopausal Med. 2021. 27: 1-7.
22. Bondi C, Ferrero S, Scala C. Pharmacokinetics, pharmacodynamics and clinical efficacy of ospemifene for the treatment of dyspareunia and genitourinary syndrome of menopause. Expert Opin Drug Metab Toxicol. 2016. 12: 1233-1246.
23. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD, on efforts to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for "vaginal rejuvenation" Accessed. 2024.
24. Varlaro VMG, Mugnaini F, Bisacci C, Fiorucci P, Rango P, et al. Carboxytherapy: Effects on microcirculation and its use in the treatment of severe lymphedema. Acta Phlebol. 2007. 8: 79-91.
25. Seidel R. Effect of carbon dioxide facial therapy on skin oxygenation. J Drugs Dermatol. 2015. 14: 976-980.
26. Khiat L, Leibaschoff GH. Clinical prospective study on the use of subcutaneous carboxytherapy in the treatment of diabetic foot ulcer. Surg Technol Int. 2018 32: 81-90.
27. Stolecka-Warzecha A, Chmielewski Ł, Deda A, Śmich A, Lebiedowska A, et al. The influence of carboxytherapy on scar reduction. Clin Cosmet Investig Dermatol. 2022. 15: 2855-2872.
28. Ferreira JC, Haddad A, Tavares SA. Increase in collagen turnover induced by intradermal injection of carbon dioxide in rats. J Drugs Dermatol. 2008. 7: 201-206.
29. Eldsouky F, Ebrahim HM. Evaluation and efficacy of carbon dioxide therapy (carboxytherapy) versus mesolipolysis in the treatment of cellulite. J Cosmet Laser Ther. 2018 20: 307-312.
30. Podgórna K, Kołodziejczak A, Rotsztejn H. Cutometric assessment of elasticity of skin with striae distensae following carboxytherapy. J Cosmet Dermatol. 2018 17: 1170-1174.
31. Nassar SO, Eltatawy RAR, Hassan GFR. Safety and efficacy of plateletrich plasma vs carboxytherapy in the treatment of atrophic scars: A comparative clinical and histopathological study. Dermatol Ther. 2020 33: e13942.
32. Oliveira SMD, Rocha LB, Cunha MTR, Cintra MMM, Pinheiro NM, et al. Effects of carboxytherapy on skin laxity. J Cosmet Dermatol. 2020. 19: 3007-3013.
33. El-Domyati M, El- H, Din W, Medhat W, Ibrahim MR, et al. Carboxytherapy for striae distensae: A promising modality. J Cosmet Dermatol. 2021. 20: 546-553.
34. Kroumpouzos G, Arora G, Kassir M. Carboxytherapy in dermatology. Clin Dermatol. 2022. 40: 305-309.
35. Lima SMRR, Honorato JV, Silva MALG. Glycine max (L.) merr isoflavone gel improves vaginal vascularization in postmenopausal women. Climacteric. 2020. 23: 505-510.
36. Warinsiriruk P, Tantitham C, Cherdshewasart W, Shobeiri SA, Manonai J. Effects of Pueraria mirifica on vaginal artery vascularization in postmenopausal women with genitourinary syndrome of menopause. Maturitas. 2022. 160: 4-10.

37. Kang B, Cai Y, Jia Z. Cell-free fat extract prevents vaginal atrophy in an ovariectomized model by promoting proliferation of vaginal keratinocytes and neovascularization. Aesthet Surg J. 2022. 42: 55-68.

Copyright: © 2024 Gustavo H Leibaschoff, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.