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Editorial

Fractional Carbon Dioxide Laser Therapy Compared to Ospemifene in the Treatment of Vaginal Atrophy in Menopause.

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Abstract

During the menopausal transition, women often experience an array of symptoms, including vaginal dryness, itching, pain, burning, decreased sexual desire, and inadequate lubrication, which are all due to hormonal changes called hypoestrogenism. Hypoestrogenism simply means a low level of estrogen which turn leads to a constellation of symptoms including hot flashes, urinary tract infections, decreased bone density and sleep disturbances. Some women find these symptoms embarrassing not to seek help, while some take it as a natural process of aging. Although various researchers have established different treatments in the past, such as lubricants and moisturizers, newer therapies such as fractional carbon dioxide (CO2) laser therapy and a selective estrogen receptor modulator ospemifene are currently being used and yet still researched. To highlight the lack of research on this topic, our article search involving only the PubMed database yielded 175 articles initially, but after exclusion and inclusion criteria, we were left with only 32 studies directly related to our research topic. Our study included English articles, full-text articles, articles on human studies, and articles from 2005-2020. We excluded all studies prior to 2005, animal studies, pediatrics study, and only abstract study. All articles were chosen without limitation to the type of study. Our review suggests that patients often present with various symptoms and severity based on histology, mechanisms, and clinical findings. Therefore, treatment should be personalized. Our study aimed to further understand a better treatment option for vulvovaginal atrophy (VVA) in postmenopausal women, knowing that menopause is an inevitable stage of a woman's life.

Ospemifene Use

Ospemifene is said to be the only selective estrogen receptor modulator (SERM) indicated for treating vulvovaginal atrophy (VVA). It was approved by the food and drug administration (FDA) in 2013 for the treatment of moderate to severe vaginal atrophy (VVA) as well as dyspareunia [14]. Ospemifene is said to exert a positive effect on the vaginal epithelium and, at the same time, not affecting other estrogen-dependent organs such as the breast and endometrium. Palacios S et al. conducted a meta-analysis on this topic in 2020 with a total of 2086 participants, which were followed up to 52 weeks, and the result confirmed ospemifene to a good choice for treating vulvovaginal atrophy (VVA) as well as having protective effects on bone health [15].

Simon J et al. also conducted a similar study on this topic. They noted that at 60 mg dose of ospemifene use, it has a beneficial effect on vaginal dryness and reduces the severity of dyspareunia. Although the common side effect noted by the 60 mg of this drug is hot flashes, but this adverse effect is said to decline after four weeks of ospemifene treatment [16]. However, this study contradicts the study by Wurz G et al., by the fact that ospemifene exerts a slight estrogenic effect on the endometrium [17]. Bruyniks N et al. conducted a survey in 2016 using a Most burdensome symptom (MBS) model to analyze an individual's symptoms. The outcome of the study demonstrated a statistical significance reduction in symptoms of women taking 60 mg ospemifene treatment [18].

Introduction & Background

Menopause is said to be the end of menstruation. The word "menopause" is coined from the Greek word 'mens' meaning 'monthly' and 'pausis' meaning 'cessation'. Menopause is a natural phenomenon every woman goes through in life when her menstrual period stops, and during these transitions, the woman's body tends to make less estrogen and progesterone [1]. As a result of the reduction in estrogen levels during menopause, women may experience various genital and urinary problems. The menopause transition is experienced by approximately two 1.5 million women each year. In an Australian population based assessment, 86% of women consulted a physician at least once to discuss menopausal symptoms [1]. These symptoms include vaginal itching and discharge, vaginal atrophy, vagina burning, urinary urgency, recurrent urinary tract infections, which is collectively known as genitourinary syndrome of menopause (GSM). However, these syndromes' constellations are less reported because some women perceive these symptoms as a natural part of aging and may not report symptoms.

However, a 50 percent rate of postmenopausal women affected by vulvovaginal atrophy (VVA) or genitourinary syndrome of menopause reports these symptoms to be burdensome to their quality of life [2,3]. To maintain the vaginal health and avoid the decline in the quality of life, various treatments of vagina atrophy are already in use. The most common first-line treatments for mild vaginal atrophy (VA) include lubrication and moisturizers. However, studies have shown that these lubrications and moisturizers provide symptomatic relief only and are insufficient in more advanced issues. Some women also report the use of lubricant as uncomfortable and inconvenient [3]. Currently, laser therapy and the use of ospemifene are newer alternatives used. Although, few studies have shown the concomitant use of both ospemifene and laser therapy as a beneficial treatment for vaginal atrophy (VA). However, the use of fractional carbon dioxide (CO2) laser therapy has been suggested as a better option to treat vaginal atrophy (VA) in postmenopausal women due to its long-term efficacy, safety, and clinical outcomes, although more research still needs to be done [3].

The study's limitation showed that some signs of most burdensome symptom (MBS) might change over time, and the less commonly experienced symptoms cannot be accounted for. We also established that this model is not practical because every woman is different and experiences things differently, so symptoms may differ between individuals. Therefore, the study lacks generalizability because the number of women that participated in the study is not a true reflection of the general population (Table 2).

Study	Year	Number of Patients	Conclusion
Palacios S et al [15]	2020	2086	Vaginal estrogen such as ospemifene alleviates symptoms and restores vaginal health.
Simon J et al [16]	2018	2200	Ospemifene use does not have any detrimental effect on bones, breast and cardiovascular system but exerts a positive effect on the vaginal.
Wurz G et al [17]	2014		Ospemifene exerts slight estrogenic effect on the endometrium but has full agonistic effect on the vaginal epithelium.
Bruyniks N et al [18]	2016	1463	Compared to placebo, ospemifene showed a great improvement in patients with moderate to severe vaginal symptoms.

Table 2: Represents the studies found discussing the use of Ospemifene.

Comparing Fractional Laser Therapy to Ospemifene

Fractional carbon dioxide (CO2) laser therapy is a new approach in managing vaginal atrophy (VA) in postmenopausal women through thermal effects on the vaginal epithelium, and so is ospemifene, which exerts its estrogenic agonism on the vaginal epithelium. While some research has shown these two therapies to be more efficient when used together, others have offered one to better than the other.

Fractional carbon dioxide (CO2) Laser Therapy and Ospemifene

According to the North American Menopause Society (NAMS), Ospemifene is the first selective non-hormonal estrogen receptor modulator (SERM) used to treat vaginal atrophy due to menopause that was food and drug administration (FDA) approved on February 26, 2013. In 2014, it was approved by the European Medical Agency (EMA) for the treatment of moderate to severe genitourinary syndrome of menopause (GSM). Although The North American Menopause Society (NAMS) suggested using this drug in treating vaginal atrophy (VA), it relieves mild to severe symptoms. However, they raised concern for drug safety in the endometrial lining in women with cancer as there are no precise data to support this population's security or safety. Many women also reported having many side effects such as increase hot flashes and an increase in symptom severity with this hormonal therapy [4]. Fractional carbon dioxide (CO2) laser therapy, on the other hand, is said to be a better alternative in the treatment of vaginal atrophy (VA) in postmenopausal women because it is well tolerated and more effective in the long-term treatment of vaginal atrophy (VA) [5]. Laser therapy was first introduced in the 1980s for other procedures such as plastic surgery, skin scarring, and aging effects. Nevertheless, recently, various types of laser therapy are in use for the treatment of gynecological problems. Hence the use of fractional carbon dioxide (CO2) laser therapy in treating vaginal atrophy (VA) in postmenopausal women [6]. The laser therapy involves high carbon dioxide (CO2) laser absorption (10,600mm) with various wavelengths. These wavelengths induce a wound process that initiates the remodeling and neoformation of elastic fibers that tighten and restore the vaginal lining [4].

Implications of Fractional CO2 Laser

The food and drug administration (FDA) approved fractional carbon dioxide (CO2) laser therapy in 2018, but after it surfaced in the market, some side effects were experienced by some women after use. The food and drug administration (FDA) warned practitioners against using this procedure because of the following adverse effects; scarring, bleeding, and worsening symptoms.

Salcedo F et al. conducted a study in 2020 with a total number of two patients. Both patient's cases reported improved sexual health while the second patient's case notably showed that after one laser application and 90 days of ospemifene use, the result revealed better vaginal color, moist /elastic epithelium with the absence of vestibular lesions, reduced dryness, and satisfying sexual intercourse. The study concluded that combined treatment with laser therapy and ospemifene is effective in treating vulvovaginal atrophy (VVA) in postmenopausal women [19]. However, we skeptical due to the sample size as it not an adequate representation of the entire population. Also, the small size can lead to decrease variability, increases the risk of non-response bias, and increases the likelihood of type II error, which decreases the power of the study. Preti M et al. conducted a study in 2019. Their study questioned the use of fractional carbon dioxide (CO2) laser therapy in treating vulvovaginal atrophy (VVA) as it hinders the patient's autonomy and choice [20]. Their study questions the safety and long-term effects of fractional carbon dioxide (CO2) laser, as well as other currently available treatments. Their research further argues that most studies on fractional carbon dioxide (CO2) laser therapy are industry-funded, which leads to a significant risk of bias. Also, they argued that most literature on fractional carbon dioxide (CO2) laser therapy is post-marketing rather than being carried out within a controlled clinical trial. Because safety must be proven before any product reaches the customer, finally, the therapeutic use of carbon dioxide (CO2) laser therapy should be evaluated in a well-designed study with an appropriate time scale, clinical or randomized, in other to assess its efficacy and safety (Table 3).

$_2$Study	Year	Number of patients	Conclusion
Salcedo F et al [19]	2020	two	Both the use of fractional carbon dioxide (CO_2) laser therapy is beneficial in treating vulvovaginal atrophy in postmenopausal women
Preti M et al [20]	2019		Fractional carbon dioxide (CO_2) laser therapy seems promising, but its long-term use and clinical application needs adequate research under a vigorous clinical or randomized control trial.

Table 3: Represents the studies found discussing the comparison between fractional carbon dioxide (CO2) laser therapy and Ospemifene.

However, other researchers have proven this procedure to be more efficient and effective in treating vaginal atrophy (VA) than other available treatments such as hormonal therapy and vaginal lubricants. Therefore, the use of high energy maintains healthy tissues and enables rapid and complete epithelial repair. More so, the histological findings after the use of the procedure show a thicker, improved epithelium and increase fibroblast activity [6,7]. The mechanism of action of this procedure is equivalent to that of radiofrequency, which involves a high-frequency current that raises the intracellular temperature to about a 100 degree, thereby amplifying the current provided as 60 cycles/second within the range of 500,000 (500KHz) to 1,500,000 cycles/second (1.5MHz), reaching the frequency of 4,000,000 cycles/second (4MHz). The high-frequency current induces its effects on the tissues without disrupting the local tissues [8]. Other available treatment options include non-hormonal vaginal moisturizer that inserts into the vaginal, vaginal lubricants, estrogen prescriptions such as vaginal ring (17-estradiol), vaginal tablet (estradiol hemihydrate), vagina cream (conjugated estrogens). Although these alternative treatments have been in use for decades, they should be used in lower dosages and used cautiously in cancer patients [9].

Finally, as women advance in age, they spend over 30% of their lives in this "inevitable" stage called menopause. These stages involve estrogen loss, decreasing blood flow to the vagina, and causes vaginal tissues to become thinner, less elastic, and dryer. Intercourse becomes more painful following bleeding and spotting as vaginal secretions decline. Therefore, it is vital to look into the problems faced during these stages of their lives. This literature will give insight into treatment options that are best for postmenopausal women to ameliorate vaginal health and symptoms.

Review

Discussion

The hypoestrogenism attributed to menopause has a significant effect on urinary and vaginal health, leading to various symptoms such as dryness, impaired sexual function, itching, pain, irritations, and burning. Vulvovaginal atrophy (VVA), a generalized term, is also associated with dysuria, urinary incontinence, and urinary tract infections [10].

Limitations

The potential limitation of this study is the lack of articles or research on this very topic. Although fractional carbon dioxide (CO2) laser therapy and ospemifene are quite known and currently being used, we realized that there's still a lack of evidence-based research on it proving its efficacy, potency, safety, and over-all use. Although our study aimed at comparing one therapy to the other, we experienced a lack of comparative literature, which would have been useful in our research. Moreover, in this research paper, only review articles from 2005-2020 were used. That is to say that quality and valuable studies beyond 2005 might have been excluded/omitted from this research. Also, we would have liked to see what the research outcome would be if animal studies were included because it might be of clinical relevance. Finally, we concluded that using only one database might have influenced our research outcome because some vital studies would have been relevant if other databases were utilized.

Conclusions

This study article aimed to discuss and analyze how fractional carbon dioxide (CO2) laser therapy compared to ospemifene is effective in the improvement of the overall sexual health of postmenopausal women with vaginal atrophy (VA). Both the use of laser therapy and ospemifene showed to be effective in treating vulvovaginal atrophy (VVA) in postmenopausal women. However, more research proved fractional carbon dioxide (CO2) laser therapy to be more effective than ospemifene. Laser therapy establishes a long-term efficacy in treating vulvovaginal atrophy (VVA) by the histological findings, which revealed an improved vaginal epithelium. More so, ospemifene demonstrated a safe and effective alternative to estrogen-based products for treating vulvovaginal atrophy (VVA) in postmenopausal women. Recommendations for the future include more platforms to raise awareness on clinical symptoms and signs to women approaching menopause so as to remove the stigma that comes with menopause. By removing this stigma, there would be more reported cases, and treatment would be sorted after. However, treatment should be tailored to individual clinical symptoms because it's stages and intensity all vary in women.

According to various research, energy-based devices have proven to be effective in revitalizing the vaginal and vulvar tissues. With the high-frequency energy, heat is induced into the vaginal region, which causes tissue remodeling, collagen contraction, and increased blood flow [11]. The use of fractional CO2 laser treatments reduces the risk of infection by restoring the mucosal tone, muscle tone, and elasticity, which improves general function and sexual health [11]. Over the years, estrogen-based methods such as lubricants, moisturizers, and drugs have been used. The recent food and drug administration (FDA) approved drug ospemifene is still being researched. The efficacy in treating vaginal atrophy (VA) in postmenopausal women is questioned due to the lack of evidence-based research. Although some literature has shown ospemifene to be useful in vaginal atrophy (VA) by improving dryness and dyspareunia, some side effects are still associated with it. Therefore, more research still needs to be done in other to prove both the efficacy and potency of the drug. While comparing and contrasting various articles, this study would look into both the use of fractional carbon dioxide (CO2) therapy along ospemifene use.

Symptoms and Clinical Findings

The initial symptom of menopause is vaginal atrophy (VA) and vagina dryness. Nappi RE and Palacios S. conducted a study in 2014, which revealed that other symptom includes epithelial thinning, soreness, stingy pain, vaginal spotting, which could be yellow or grey with watery discharge and increased pH. They also noted that the women might not know the symptoms of vaginal atrophy (VA) because they are either self-treating, embarrassed or might see it as less vital but would eventually report cases of vagina discharge or urinary urgency [2]. Alvis et al. also conducted a study in 2019; the study showed that the leading cause leading to clinical symptoms is a drop in circulating estrogen levels, which causes flattening of epithelial surfaces. The decrease in estrogen level also involves a decrease in type I/III collagen ratio, which leads to low tissue strength. Other symptoms involve epithelial thinning, which increases the incidence of trauma, bleeding, and ulceration. They noted that the thinning of the vaginal tissue exposes the connective tissues to infection and inflammation [10].

Additionally, more prospective study is needed on both fractional carbon dioxide (CO2) laser therapy and ospemifene in other for subjects to be followed longitudinally over time and results collected in time to minimize recall error and avoid selection bias. This article is useful in the sense that it contributes to the proper long-term treatment of vulvovaginal atrophy (VVA) in postmenopausal women. Finally, despite the lack of literature on treatments of vulvovaginal atrophy (VVA) with fractional carbon dioxide (CO2) laser and ospemifene, we still established that these symptoms are under-diagnosed, under-addressed, under-treated, irrespective of the newer and adequate therapy available, which results in a low quality of sexual health in many postmenopausal women.

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Clinical Findings

The clinical findings observed by Nappi RE and Palacios S. showed an atrophied vaginal introitus. The vaginal mucosa appeared shiny, red, and inflamed with vagina narrowing and shortening [2]. Other clinical findings include loss of elasticity, insufficient hydration, fibrosis, labia agglutination, loss of pubic hair, and burning sensation, leading to physical, chemical, and mechanical damage.

Histological Findings

The vaginal tissue is composed of multiple layers of squamous cells and four histological layers, including the stratified squamous epithelium, elastic lamina propria, fibromuscular layer, and the adventitia. Our study is trying to evaluate the changes in the histology of the vaginal tissue with various treatment options for postmenopausal women with vaginal atrophy (VA).

We believe the use of fractional carbon dioxide (CO2) laser therapy has long-term efficacy in treating vaginal atrophy (VA). However, we do not think that the service of ospemifene is more efficient in treating this condition. Samuel J et al. conducted a prospective study on this topic in 2019 with a total number of 43 postmenopausal women, in which 40 received all treatment and completed both six months and 12 months follow-up. Samuel J et al. concluded that the biopsy results from the use of fractional carbon dioxide (CO2) laser treatments showed an increase in collagen deposits, elastin staining, thicker epithelium with increased cell layers, and increased submucosal vascularity. More so, the outcome showed normalization of pH as well restoration of local lactobacilli, an organism that maintains the metabolism and normal function of the vaginal. This study's main limitation is a lack of a control arm to give account for a placebo effect and a comparison therapy [11]. Eder S et al. also analyzed the histological reports of biopsy before and after treatments in postmenopausal women with vaginal atrophy. The after-treatment of their study in 2018, which consisted of 28 patients, showed a thicker epithelium, increase in fibroblast activity, regeneration of vaginal mucosa, increased collagen, restoration of glycogen, and increased micro-vessel circulation [12].

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Although the studies conducted by Samuel J et al. and Eder S et al. proved the effectiveness of fractional carbon dioxide (CO2) therapy in treating vaginal atrophy, we were more concerned about the sample size used, which left us to ask if it can represent the general population. o Additionally, with the patients being treated three times at four weeks interval, we also noted that this procedure might not be cost-effective for the general population since it has to be repeated several times to achieve the desired goal (Table 1).

Study	Year	Number of patients	Conclusion
Samuel J et al [11]	2019	43	Fractional carbon dioxide (CO_2) laser treatment provides a long-lasting treatment for menopausal patients with vaginal atrophy.
Eder S et al [12]	2018	28	Fractional carbon dioxide (CO_2) laser therapy can be considered a therapeutic option for postmenopausal women suffering from vaginal atrophy.

Table 1: Represents the studies found discussing histological changes with Fractional carbon dioxide (CO2) laser therapy.

Mechanism of Action of laser CO2

According to Santoro N., 2016, the mechanism of the laser CO2 involves the induction of a local heat shock effect, which is followed by rapid and transient changes in cellular metabolism. The heat-induced damage produces an expression of various growth factors, which stimulates new collagen synthesis at the treated sites [13]. Santoro N, also describes the menopausal mechanism as a stage to stage transition which encompasses of stage 3a and 3b as the stage were fertility is low with fluctuation of ovarian reserve. In this stage, women do not significantly see a change in their menstrual cycle because the follicular stimulating hormone (FSH) is often normal or slightly elevated. The stage 2b is the stage were the ovarian follicles shrinks. In this stage, the follicular stimulating hormone (FSH) is consistently elevated and women tend to experience a decline in their menstrual cycle greater than seven days after a missed menses. The final stage which is the stage 1 is the late transitional stage were menstrual cycle become irregular and menstrual periods are scarce with low circulating estrogen, long periods of amenorrhea and great increase in menopausal symptoms.

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The studies concluded that the various stages from the transition of pre-menopausal to menopausal is challenging for women. Although the study involved multiple women from different ethnicity in Melbourne region, we are concerned that the same analysis might not be reproduced in another region. Another mechanism of the laser CO2 involves a wavelength of 10,600nm that is high enough to exert a 5J/cm2 absorbent upon the skin surface. Then after, the skin contracts and the fibers in that area shrinks (Figure 1) [13].

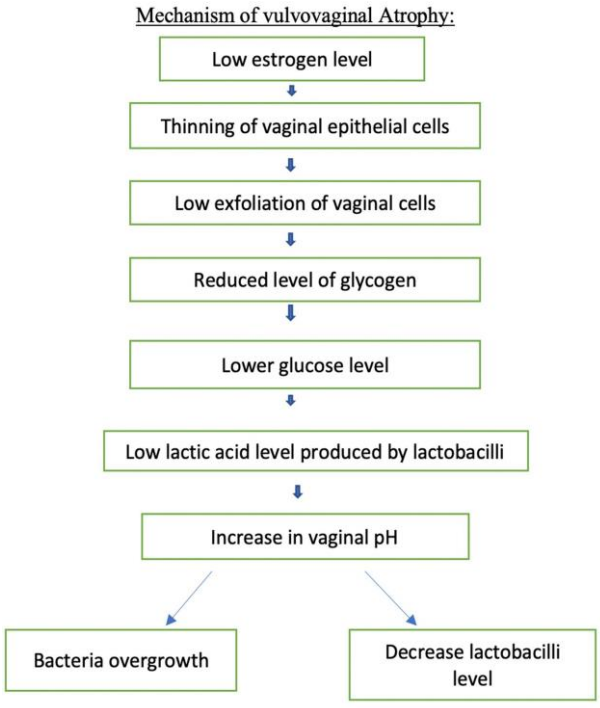

Figure 1: The mechanism of vulvovaginal atrophy in postmenopausal women.

Fractional Carbon Dioxide Laser Therapy Compared to Ospemifene in the Treatment of Vaginal Atrophy in Menopause.

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