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Treatment of Genitourinary syndrome of menopause with Erbium:YAG laser: a prospective study of efficacy and safety of the treatment for women after menopause of natural origin and therapy-induced menopause in breast cancer survivors.

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ABSTRACT

Introduction: Genitourinary syndrome of menopause (GSM) affects up to 50% of postmenopausal women. It can be especially severe in breast cancer survivors after therapy-induced menopause. The aim of this study was to collect data on the safety, efficacy and satisfaction of patients with Er:YAG laser vaginal treatment and to assess whether the result of the laser treatment for GSM is similar when performed either in women after menopause induced by treatment of breast cancer or in women after natural menopause.

Patients and methods: 40 patients with genitourinary syndrome of menopause were admitted in the study: 20 patients with no history of breast cancer (group A) and 20 patients with a history of breast cancer (group B). The patients in group A were randomly divided into two sub-group A1 and A2. Patients in group A1 received vaginal preparation with 0,5mg estriol topically 3 times per week for 2 weeks before laser treatment to hydrate the vaginal mucosa. Patients in group A2 and B received vaginal preparation with platelet rich plasma (PRP) injections two weeks before laser treatment. After vaginal preparation all three groups of patients were treated with 2 sessions of RenovaLase laser treatment (2940nm Er:YAG laser in non-ablative mode). Patients were followed for 12 months. The effects of laser on dyspareunia, dryness and frequency of intercourse avoidance were assessed. Patients were also asked about their satisfaction with the treatment.

Results: Statistically significant reduction of vaginal dryness and dyspareunia was observed in all three groups at all follow-ups up to 12 months post-treatment. Also improvement in patients' sexual life measured by patient evaluation of intercourse avoidance was statistically significant in all three groups at all follow-ups. There were no serious side effects noted. Patients were highly satisfied with the treatment.

Conclusion: Laser treatment is successful in reducing GSM symptoms in women with natural menopause and also in women with therapy-induced menopause.

Key words: genitourinary syndrome of menopause, GSM, menopause, vaginal laser treatment, breast cancer, vaginal dryness, dyspareunia.

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I. INTRODUCTION

Menopause is an irreversible part of the female aging process. It can occur also prematurely due chemotherapy or other medical interventions. In this case we are talking about therapy-induced menopause.

Almost 50% of postmenopausal women are affected by genitourinary syndrome of menopause (GSM).[1] Since 2014 GSM is defined as: "a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections."[2] It seems that the prevalence of GSM is even higher in breast cancer survivors, after therapy-induced menopause.[3]

There are different treatment options available to reduce the symptoms of GSM, among them lubricants and moisturizers, vaginal estrogen therapy, systemic estrogen therapy (when prescribed for vasomotor symptoms) and ospamifene.[4] Additionally, recent studies have shown that vaginal erbium laser treatment is able to induce long-lasting improvement of GSM symptoms.[5, 6]

Vaginal estrogen therapy is widely used for the treatment of GSM. However, special caution should be made in management of estrogen-dependent tumors, since there is initial elevation in circulating

estrogen levels, following vaginal estrogen application.[7] In a study by Kendall et al. further concerns have been raised regarding the use of vaginal estrogen therapy for postmenopausal breast cancer survivors treated with aromatase inhibitors, since vaginal estrogen therapy in short term raises levels of systemic estradiol.[8] Anyhow, a lot of breast cancer survivors, in spite of the presence of severe GSM symptoms avoid medications containing estrogen, due to the fear of the recurrence of disease.[9]

The main benefit of laser therapy, beside its non-invasiveness, is that it can be safely used for patients who have estrogen contraindicated. Gambacciani et al. showed that erbium laser is safe and effective treatment option for breast cancer survivors affected by GSM.[10] In a recent study published by the same authors, it has been shown that effects of laser therapy on bothersome symptoms of vaginal dryness and dyspareunia in breast cancer survivors are long-lasting (statistically significant decrease of symptoms for up to 12 months).[11]

The mechanism of action is the release of sequential Er:YAG SMOOTH mode laser pulses that leads to a controlled rise in tissue temperature, causing mild hyperthermia. Mucosa is warmed to around 45°C, inducing neocollagenesis, increase of cell proliferation, and anti-inflammatory action.[12]

The effect of laser treatment is better if vaginal tissue is hydrated. For this purpose local vaginal estrogen treatment (for patients with no contraindication to estrogen) or platelet-rich-plasma (PRP) injected intravaginally can be used. According to Marx, PRP is: "a volume of autologous plasma that has a platelet concentration above baseline."[13] It is prepared from patient's own blood, so there is no possibility of disease transmission.[13] Platelets inside PRP secrete 7 protein growth factors that are involved in wound healing.[14]

The first objective of this study was to collect data on the safety, efficacy, and satisfaction of patients with laser treatment of GSM. Another objective was to assess whether the result of the treatment differ between women with menopause induced by treatment of breast cancer and women after natural menopause.

We have previously published the results of 3 months follow up.[15] Here we are presenting extended follow up data at 6, 9 and 12 months.

II. PATIENTS AND METHODS

Treatment was applied to patients with GSM after natural menopause or patients with GSM with therapy-induced menopause (breast cancer survivors). All treatments were ambulatory, performed from October 2013 to January 2015.

The research protocol was approved by Ethics Committee of the Clinical Research Center Foundation, in Medellin, Colombia. All patients provided written informed consent.

Detailed info about inclusion and exclusion criteria and treatment protocol can be found in our previous publication with shorter follow up.[15]

40 patients with GSM were enrolled in the study: 20 patients with no history of breast cancer (group A) and 20 patients with a history of breast cancer (group B). 20 patients from group A were further randomly divided into two sub-groups (A1 and A2). The vaginal preparation was carried out with hormones for group A1 (estriol ovules- Esteine, for 2 weeks before laser treatment, 0,5 mg topical 3x/week). Groups A2 and B received vaginal preparation with PRP (Injection of PRP (2-3 cc of PRP) applied to the multiple injection sites on vaginal wall 2 weeks prior treatment).

Two weeks after vaginal preparation all three groups were treated with a first sessions of RenovaLase laser treatment (2940 nm Erbium YAG laser – Fotona XS Dynamis). Three weeks later, the second laser treatment session was performed. The parameters used were in accordance with RenovaLase® treatment protocol (treatment of vaginal canal: 5,5Jcm2, 1,6HZ, 7mm spotsize; treatment of introitus and vestibulum: 10J/cm2, 1,6Hz, 7mm spotsize). Local topical anesthesia (2% Lidocaine chlorhydrate gel) was used prior to laser treatment (applied on vestibulum and introitus).

At each follow up visit GSM symptoms (dryness, dyspareunia) were evaluated and patient satisfaction with treatment was assessed. The symptoms were assessed on a 4-point scale: 0-no symptoms, 1-mild symptoms, 2-moderate symptoms and 3-severe symptoms. Patients were also asked about sexual intercourse avoidance. The frequency of intercourse avoidance was assessed on a 4-point scale: 0-never, 1-rarely, 2-often, 3- always. Patient satisfaction was assessed with a questionnaire where two options were given (satisfied, not satisfied).

Patients were followed up for any adverse effects at 3, 6, 9 and 12 months follow up.

Statistical analysis was performed using the SPSS statistical package (IBM Statistics SPSS Version 23).

III. RESULTS

At enrollment all patients were affected by severe dyspareunia and vaginal dryness (Table 1, Table 2). 39 patients (of 40) marked "always" when asked about frequency of intercourse avoidance (Table 3). Only one patient from group B reported never avoiding intercourse. Detailed description of patient's characteristic at enrollment can be found in our previous publication.[15]

Vaginal dryness improved in all patients (Table 1). Before the treatment all patients had severe vaginal dryness. 12 months after the treatment 60% of patients in the A1 subgroup were asymptomatic and 40% of patients improved from severe to mild or moderate dryness. In A2 subgroup 30% were asymptomatic and 70 % had mild vaginal dryness 12 months after treatment. In the group B 65% of patients become asymptomatic and 35 % of patients remained with mild or moderate vaginal dryness. The results of vaginal dryness improvement at 3, 6, 9 and 12 months follow up are given in Table 1.

Mean values of vaginal dryness assessed on the severity scale from 0 to 3 show statistically significant reduction of symptoms ($p<0.001$ for group A1, A2 and B) in all three groups of patients up to 12 months follow up. More details are presented in Fig. 1.

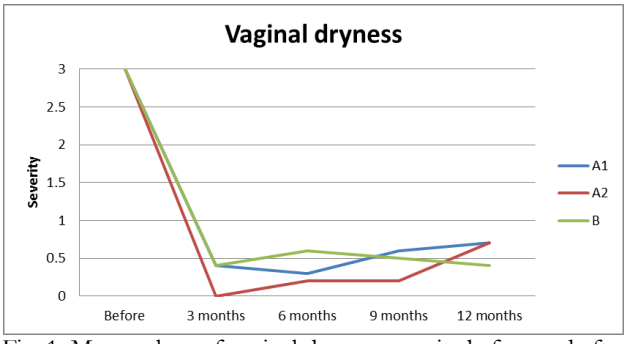

Fig. 1: Mean values of vaginal dryness severity before and after the laser therapy: The symptoms are assessed on a scale 0-3 as follows: 0-no symptoms, 1-mild symptoms, 2-moderate symptoms, 3-severe symptoms in A1, A2 and B group before the treatment and after 3, 6, 9 and 12 months after treatment.

Before the treatment all patients had severe dyspareunia. At 3 months follow up all patients in group A2 and B and 60% of patients from group A1 were asymptomatic, and 40% patients from group A1 had mild dyspareunia. At 12 months follow up there were no patients with severe dyspareunia in groups A2 and B. The effect of laser treatment on dyspareunia was less permanent in group A1 where 40% of patients were

Table 1: Vaginal dryness results.

Group	Severity	Baseline	Follow up in months after Tx2			
			3 months	6 months	9 months	12 months
A1 (n=10) menopausal, pre-op: estriol	No symptoms	0%	60%	70%	70%	60%
	Mild	0%	40%	30%	0%	10%
	Moderate	0%	0%	0%	30%	30%
	Severe	100%	0%	0%	0%	0%
A2 (n=10) menopausal, pre-op: PRP	No symptoms	0%	100%	80%	80%	30%
	Mild	0%	0%	20%	20%	70%
	Moderate	0%	0%	0%	0%	0%
	Severe	100%	0%	0%	0%	0%
B (n=20) post breast cancer, pre-op: PRP	No symptoms	0%	60%	50%	55%	65%
	Mild	0%	40%	45%	40%	30%
	Moderate	0%	0%	0%	5%	5%
	Severe	100%	0%	5%	0%	0%

Table 2: Dyspareunia results

Group	Severity	Baseline	Follow up in months after Tx2			
			3 months	6 months	9 months	12 months
A1 (n=10) menopausal, pre-op: estriol	No symptoms	0%	60%	70%	30%	40%
	Mild	0%	40%	30%	10%	0%
	Moderate	0%	0%	0%	30%	30%
	Severe	100%	0%	0%	30%	30%
A2 (n=10) menopausal, pre-op: PRP	No symptoms	0%	100%	100%	50%	60%
	Mild	0%	0%	0%	50%	40%
	Moderate	0%	0%	0%	0%	0%
	Severe	100%	0%	0%	0%	0%
B (n=20) post breast cancer, pre-op: PRP	No symptoms	0%	100%	60%	65%	55%
	Mild	0%	0%	30%	25%	40%
	Moderate	0%	0%	5%	10%	5%
	Severe	100%	0%	5%	0%	0%

asymptomatic 12 months after treatment, 30% of patients stayed with moderate dyspareunia and 30% of patients again presented with severe dyspareunia. In group A2 60% were asymptomatic after 12 months and 40% of patients stayed with mild pain. In group B 55% were asymptomatic after one year and 45% of patients still had mild or moderate dyspareunia. The effect on dyspareunia seems to decrease in A1 subgroup already after 9 months with the percentage of asymptomatic patients falling from 70% at 6 months to 30 % at 9 months. The effect of laser treatment on dyspareunia is presented in Table 2.

There was a statistically significant reduction of mean values of dyspareunia assessed on the severity scale in all three groups at 3, 6, 9 and 12 months follow up. However the relief of symptoms at 12 months after treatment is more prominent in A2 ($p<0.001$) and B group ($p<0.001$), although it is still statistically significant also in group A1 ($p=0.007$). More details are presented in Fig. 2.

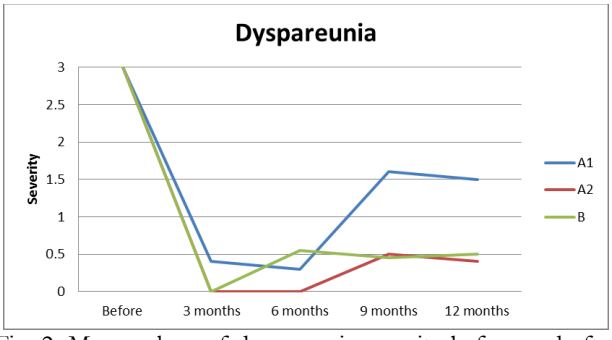

Fig. 2: Mean values of dyspareunia severity before and after the laser therapy: The symptoms are assessed on a scale 0-3: 0-no symptoms, 1–mild symptoms, 2–moderate symptoms, 3–severe symptoms in A1, A2 and B group before the treatment and after 3, 6, 9 and 12 months after treatment.

The improvement of the patients' sexual life was dramatic especially in a group A2. At 3, 6, 9 and 12 months after the therapy 100% of patients reduced intercourse avoidance from always to never. In a group A1 6 months after treatment 70% of patients never avoided intercourse and 30% avoided it only rarely, however 12 months after treatment 40% of patients never avoided intercourse, but 60% always did. In group B 3 months after treatment 100% of patients never avoided intercourse and 12 months after treatment 85% of patients never avoided intercourse, remaining 15% avoided intercourse only rarely. The improvement of the patients' sexual life is presented in Table 3.

There was statistically significant reduction of mean values of frequency of intercourse avoidance in all three groups at 3, 6, 9 and 12 months follow up. The reduction of frequency of intercourse avoidance at 12 months follow up is more prominent in groups A2 and B ($p<0,001$) but it is still statistically significant reduced also in group A1($p=0,037$). More details are presented in Fig. 3.

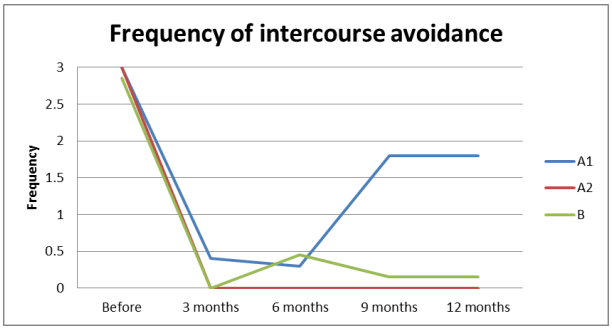

Fig. 3: Mean values of frequency of intercourse avoidance before and after the laser therapy: The frequency of intercourse avoidance is assessed on a scale 0-3: 0-never, 1-rarely, 2-often, 3-always in A1, A2 and B group before the treatment and after 3, 6, 9 and 12 months after treatment.

At 12 months post treatment, all patients from the group A2 and B reported high satisfaction not only with the treatment, but also with the results. In the group A1 3 patients were not satisfied with the result of the treatment at 9 and 12 months follow up. This might be the result at of diminishing effect of laser treatment at extended follow up.

At the first follow-up a few transient adverse effects were reported: 2 patients from group B reported mild pain, 3 patients from group A2 and 2 patients from

Table 3: Frequency of patients avoiding intercourse.

Group	Frequency	Baseline	Follow up in months after Tx2			
			3 months	6 months	9 months	12 months
A1 (n=10) menopausal, pre-op: estriol	Never	0%	60%	70%	40%	40%
	Rarely	0%	40%	30%	0%	0%
	Often	0%	0%	0%	0%	0%
	Always	100%	0%	0%	60%	60%
A2 (n=10) menopausal, pre-op: PRP	Never	0%	100%	100%	100%	100%
	Rarely	0%	0%	0%	0%	0%
	Often	0%	0%	0%	0%	0%
	Always	100%	0%	0%	0%	0%
B (n=20) post breast cancer, pre-op: PRP	Never	5%	100%	80%	85%	85%
	Rarely	0%	%	5%	15%	15%
	Often	0%	0%	5%	0%	0%
	Always	95%	0%	10%	0%	0%

group B reported burning and 2 patients from group A1 reported itching. There was no report of pain, bleeding, swelling, bruising or infection. At 3 months follow-up, there were no adverse effects reported. The symptoms of pain, burning and itching were also monitored at 6, 9 and 12 months follow up. On these follow ups some patients complained about pain, vaginal burning and vaginal itching as shown in Table 4. All these symptoms are most probably related to diminishing of the effect of the treatment and reappearing of GSM.

IV. DISCUSSION

The main goal of GSM treatment is to relieve the bothersome symptoms such as dyspareunia and vaginal dryness.

The beneficial effect of vaginal laser treatment on GSM symptoms have been previously described by Gaspar et al. where a fractional CO_2 laser was used for the vaginal rejuvenation. In their study patients' sexual function was evaluated with sexual health questionnaire. Following laser treatment there was a significant decrease of discomfort during sexual intercourse. Additionally improvement of vaginal mucous histology has been observed in most patients.[16] Salvatore et al. also showed that fractional CO_2 laser was effective to improve symptoms of GSM (among them also vaginal dryness and dyspareunia) up to 12 weeks after treatment.[17]

In contrast to CO_2 laser that work by vaporizing superficial layer of mucosa tissue [18], Er:YAG laser works without any superficial ablation. GSM treatment with Er:YAG is based on warming the mucosa with the aim to stimulate cell proliferation, neocollagenesis and neoangiogenesis. [6, 12]

The results of this study showed that vaginal treatment with Er:YAG laser (RenovaLase®) significantly reduces the symptoms of GSM – vaginal dryness and dyspareunia in patients after menopause of natural origin and patients with therapy-induced menopause for up to 12 months after treatment. These findings are consistent with the results of other studies that examined the efficacy of erbium vaginal laser for treatment of GSM. [5,6]

Gambacciani et al. assessed the effects of vaginal erbium laser in comparison to standard treatment with intravaginal estriol gel in postmenopausal women with GSM symptoms. Significant decrease of VAS (visual analogue scale) for vaginal dryness and dyspareunia was observed in both groups, however these effects lasted up to the 6 months of the observation period in laser group, but diminished in estriol group soon after discontinuation of estriol treatment.[5] The effectiveness and safety of vaginal erbium laser was also evaluated in the treatment of GSM in postmenopausal breast cancer survivors. In the study of Gambacciani et al. vaginal dryness and dyspareunia VAS scores significantly decreased after laser treatment and stayed decreased during 3 months follow up.[10] In the study of Gaspar et al. statistically significant reduction of symptoms (vaginal dryness, dyspareunia and irritation) was observed up to 18 months after laser treatment. However, it is worth to mention a trend to diminishing effect of the laser treatment at the last (18-month) follow up.[6]

As in the study of Gaspar et al. mentioned above, we also observed a diminishing of the effect of laser treatment during prolonged follow up. A minority of patients presented with diminishing of the effect and reoccurrence of symptoms of GSM already 6 months after treatment. We also asked patients for symptoms of pain, vaginal burning and vaginal itching. Some women had these symptoms immediately after laser treatment, but none of them was present 3 months after treatment. However on later follow ups these symptoms started to reappear. They are probably related to diminishing of the effect of the laser treatment and returning of GSM

Table 4: Pain, vaginal burning and vaginal itching results

Patient group	3 weeks after Tx1	3 months after Tx2	6 months after Tx2	9 months after Tx2	12 months after Tx2
A1 (n=10) (menopausal, pre-op: estriol)	Mild vaginal itching (20%)	None	Mild pain (30%), Mild vaginal burning (30%), Mild vaginal itching (30%)	Mild pain (30%), Mild vaginal burning (30%), Mild vaginal itching (30%)	Moderate pain (30%), Moderate vaginal burning (30%), Moderate vaginal itching (30%)
A2 (n=10) (menopausal, pre-op: PRP)	Mild vaginal burning (30%)	None	None	Mild vaginal burning (30%)	Mild vaginal burning (20%), Mild vaginal itching (20%)
B (n=20) (post breast cancer, pre-op: PRP)	Moderate pain (10%), Mild or moderate vaginal burning (10%)	None	Mild or moderate pain (15%), Mild or moderate vaginal burning (20%), Mild or moderate vaginal itching (40%), Severe vaginal itching (5%)	Mild vaginal burning (15%), Mild vaginal itching (35%), Severe vaginal itching (5%)	Mild pain (10%), Mild vaginal burning (15%), Mild vaginal itching (50%), Severe vaginal itching (5%)

symptoms during prolonged observation.

Since this is a non-invasive treatment, with few mild side effects we would recommend repeating the treatment after the symptoms reoccur. Long term experiences with the same Er:YAG laser modality in aesthetic and dermatology showed that these treatments can be safely repeated multiple times.

Er:YAG laser treatment is of special importance because it can offer a relief of GSM symptoms in patients with a history of breast cancer, where intake of estrogen preparations is risky. Although over-the-counter treatments may work for women with mild symptoms, they are often inadequate for women with moderate to severe symptoms. In this study we have shown that with RenovaLase® treatment we can achieve relief of symptoms of dyspareunia and dryness in this patient group up to 12 months follow up. Also in previous studies has been shown that erbium laser is safe and effective for the treatment of GSM in postmenopausal breast cancer survivors.[10] The effects of laser treatment in this population of women are comparable with the effects of treatment for women with menopause of natural origin.

In this study we used two different methods of pre-treatment vaginal preparation. It seems that the use of PRP as vaginal preparation prolongs the effect of vaginal laser therapy on dyspareunia but has lesser effect on vaginal dryness. In literature the effects of PRP have been described to promote the natural healing process. [13, 19]

To summarize, the beneficial effect of vaginal erbium laser treatment of GSM has been shown in all groups of patients (natural menopause and therapy-induced menopause). This is shown by a majority of patients that are asymptomatic at 12 months after treatment and highly satisfied with the treatment. Also, the results of treatment are comparable for patients undergone natural menopause and patients after therapy-induced menopause following breast cancer treatment.

V. CONCLUSIONS

Our study suggests that erbium laser vaginal treatment could effectively and safely be used to treat GSM symptoms in patients after menopause of natural origin as well as patients with menopause induced by breast cancer treatment. The effects of the treatment are in a majority of the patients still present 12 months after treatment, however in some patients effects diminished with time. In these patients a maintenance treatment after symptoms reappear could be an option. However, controlled studies with larger sample sizes are required to confirm the results.

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