Fractional CO_2 Laser for Vulvovaginal Atrophy

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Objective: *To evaluate the short term efficacy and safety of Fractional CO_2 laser for the treatment of vulvovaginal atrophy.*
Material and Method: *From March 2015 to October 2015, 112 menopausal women were recruited. All women with VVA were treated by using Fractional CO_2 laser; power 30 watts, 1-3 stacks with 360° vaginal probe for 3 consecutive times, 4 weeks apart. Before laser treatment, the subjective measurement of VVA symptoms was evaluated by using a questionnaire and the objective measurements were evaluated by using pH paper and VMI. Visual analog pain-score was used to scaling their discomfort during and immediately after each treatment. At 3 months after the last procedure, the subjective and objective measurements were re-assessed. Any short-term and long-term adverse events were recorded. Statistical analysis was performed by using SPSS program with p-value <0.05.*
Results: *The median of pre-screening VVA symptom score was 4 and the most bothersome symptom was the "feeling of dryness around vulvar". There was a significant reduction of the score after laser treatment. The average percentage of pre-treatment VMI was 34.7±16.1% and at one and three months after complete laser course, it was significantly increased with the mean change of 25.0±12.2% and 34.8±15.5%, respectively. For the vaginal pH, the average pH before treatment was 7.5±1.0 and the average decrement after 3 months was 0.9±1.3 with statistical significance, p-value <0.01. There were no serious complications and all were satisfied with the treatment.*
Conclusion: *Fractional CO_2 laser could ameliorate the VVA symptoms with at least 3 months of long lasting improvement of vaginal health with safety.*

Keywords: *Vulvovaginal atrophy, Fractional CO_2 laser, Efficacy, VMI*

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Vulvovaginal atrophy (VVA), manifest as a pale and thin vaginal mucosa, causes a decreasing of estrogen levels. The vaginal maturation index (VMI) can be used to measure the degree of maturation attained by the vaginal epithelium. During menopause, the proportion of the superficial and intermediate cell will decrease and the proportion of parabasal cell will increase[1]. The vaginal pH will increase and the pathogenic bacteria will overgrow resulting in frequent vaginal infections[2]. Topical estrogen has been reported to be the most effective treatment for VVA and it can remodel atrophic mucosa back to normal[3]. Increasing the proportion of superficial cells with high glycogen content can promote growth of Lactobacilus bacteria and decrease vaginal pH[4]. However, the local vaginal administration of estrogen needs to be used with caution especially for the women with hormone-sensitive cancer, liver failure and thromboembolic disease[5]. Alternative treatments include non-hormonal treatments, vaginal moisturizer or lubricants; regular sexual intercourse may also be the option[6].

Fractional CO_2 laser has been widely used for the skin rejuvenation on different parts of human body with low complication rates[7]. Recently, with a new technology of vaginal probe, this laser could significantly improve the vaginal atrophy which was confirmed by the studies using Vaginal Health Index Score (VHIS)[8] and histological data[9]. In Thailand, fractional CO_2 laser for treatment of vaginal atrophy is a new technology and never been used for VVA treatment before. The aims of this study were to evaluate the short-term efficacy and safety of Fractional CO_2 laser for the treatment of VVA and to be a pilot study in Thai women for further studies.

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Material and Method

This is a prospective single-arm clinical trial study, performing in 112 menopausal women with

vulvovaginal atrophic symptoms, who had attended the gynecology clinic at Thammasat University Hospital. The present study was approved by the Human Ethics Committee of Thammasat University. All women signed the informed consent. Inclusion criteria were the menopausal women who had VVA symptoms such as vaginal dryness, burning sensation, itching and dyspareunia and could be staying in the lithotomy position for at least 5 minute. The exclusion criteria were the women who had pelvic organ prolapses greater than stage II, severe vaginal infection, history of difficult or obstructed voiding, and any medical conditions including multiple sclerosis, Parkinson's disease, stroke, anomalies of spine and lower back, bleeding disorder and immuno-compromised host. The women who take any kinds of estrogen should be stop taking at least 6 months before the study.

All participants were treated with Fractional CO_2 laser; power 30 watts, Dot dwelling time 1,000 µs, Dot spacing 1,000 µm, 1-3 stacks with 360° vaginal probe for 3 consecutive 4 week-apart episodes (visit I-III). At the pre-screening visit (visit I) and the follow-up visits (0ne-month after the third laser = visit IV and 3-month after third laser = visit V), the VVA symptom-score, vaginal pH and VMI were recorded. After the insertion of a non-lubricated sterile vaginal speculum, 2 cm of the pH strip was placed directly to the lateral vaginal wall for 5 seconds or until moistened. The color of the strip was compared with the colorimetric scale on the enclosed card and the pH value was recorded. Then the cytology smear was collected from the upper one third of the lateral vaginal wall using the Ayre's spatula. The percentages of parabasal cells to intermediate cells to superficial cells were multiplied by its assigned value (a value of 1 to superficial cell, 0.5 to intermediate cell and 0 to parabasal cell)[10]. Immediately after all treatments, the women were asked to give the score of their discomfort during the treatment by using the visual analog pain-score and any adverse events were recorded. Patient satisfaction was assessed at each visit.

The statistical analyses were performed by using SPSS program. The *p*-value of less than 0.05 was considered statistically significant. Data from questionnaire were analyzed using descriptive statistics. Kolmogorov-Smirnov goodness of fit test was used to assess the normality of the data. Normal distributed data were then analyzed using paired t-test and repeated measure ANOVA. Friedman tests and Wilcoxon signed ranks test were used to analyze the non-normal distributed data and categorical scale data.

Results

One hundred and twelve women with vulvovaginal atrophy were recruited for the present study. Mean $\pm$ SD of age was 61.0$\pm$7.0 years with the mean $\pm$ SD of the duration of menopausal period was 12.7$\pm$8.3 years. The most bothersome VVA symptom was the feeling of dryness around vulva. The mean body weight $\pm$ SD of all these women was 58.8$\pm$8.0 kilograms and the mean height $\pm$ SD was 156.4$\pm$5.4 centimeters. One hundred and six women (94.6%) are multiparous and 82 women had vaginal delivery.

In the pre-screening visit, the median (IQR) of the VVA symptom score was equal to 4 (2-7) and the most common VVA symptom was the feeling of dryness around vulvar (87.5%). The symptom of vulvar irritation was the second most common bothersome symptom. One month after treatment with Fractional CO_2 laser (visit II), the median (IQR) score of VVA was significantly decreased to 1 (0-2). And these median scores were equal to 0 in visit III, IV and V. The Table 1 shows the percentage of all VVA symptoms in each visit with the statistical significant change when compare to the first visit, $p<0.05$.

VMI data were assessed for normality using Kolmogorov Smirnov Goodness of Fit test, and found that the data did not distribute normally. The VMI data between each visit were then compared by using the Friedman Tests. The mean $\pm$ SD of VMI of the pre-screening visit was 34.7$\pm$16.1% compare to 59.7$\pm$12.4% in the visit IV and 69.5$\pm$9.9% in the visit V. The mean difference between visit I and visit IV (one-month after complete laser course) was 25.0$\pm$12.2% and between visit I and visit V (3-month after complete laser course) was 34.8$\pm$15.5%. Results revealed that there were statistically significant increment of VMI after complete the laser course ($p<0.01$).

For the vaginal pH, the data were assessed for normality using the Kolmogorov Smirnov Goodness of Fit test, $p<0.05$. It was found that the data were not normal distribution. The Friedman test was used to compare the vaginal pH from each visit and the results revealed statistically significant differences among the data ($p<0.01$). After complete the laser course, there was a significant decrement of vaginal pH in one-month with an average decrement of 0.8$\pm$1.2 and in 3-month with the average of 0.9$\pm$1.3. Table 2 shows the objective measurements of the efficacy of Fractional CO_2 laser.

After each treatment by Fractional CO_2 laser, the participants were asked about the possible side effects including vaginal irritation, inflammation or bleeding from the vagina. It was found that no

Table 1. The percentage of VVA symptoms

VVA symptoms	Visit I n (%)	Visit II n (%)	Visit III n (%)	Visit IV n (%)	Visit V n (%)
1) Itching around vulvar (n = 112)	52 (46.4)	12 (10.7)	12 (10.7)	0 (0)	7 (6.3)
2) Burning sensation around vulvar (n = 112)	38 (33.9)	24 (21.4)	8 (7.1)	12 (10.7)	8 (7.1)
3) Painful vulvar (n = 112)	29 (25.9)	5 (4.5)	0 (0)	0 (0)	0 (0)
4) Vulvar irritation (n = 112)	65 (58.0)	39 (34.8)	0 (0)	0 (0)	0 (0)
5) Feeling of dryness around vulvar (n = 112)	98 (87.5)	26 (23.2)	9 (8.0)	15 (13.4)	6 (5.4)
6) Abnormal vaginal discharge (n = 112)	12 (10.7)	5 (4.5)	0 (0)	0 (0)	0 (0)
7) Foul smell from vagina (n = 112)	18 (16.1)	1 (0.9)	8 (7.1)	0 (0)	4 (3.6)
8) Worry about vaginal abnormality (n = 112)	42 (37.5)	9 (8.0)	0 (0)	18 (16.1)	9 (8.0)
9) Symptoms around vulvar affected SI (n = 46)	36 (32.1)	6 (5.4)	2 (1.8)	0 (0)	0 (0)
10) Symptoms around vulvar leads to pain during SI	38 (33.9)	20 (17.9)	13 (11.6)	21 (18.8)	14 (12.5)
11) Symptoms around vulvar leads to dryness during SI	43 (38.4)	20 (17.9)	2 (1.8)	0 (0)	0 (0)
12) Symptoms around vulvar leads to bleeding during SI	7 (6.3)	0 (0)	0 (0)	0 (0)	0 (0)
The median of VVA score (IQR)	4 (2-7)	1 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)

Friedman test, $p<0.05$

Table 2. The objective measurements for the efficacy of Fractional CO_2 laser

Visit	Visit I (pre-treatment)	Visit IV (1 mo-post-treatment)	*p*-value*	Visit I (pre-treatement)	Visit V (3 mo-post-treatment)	*p*-value*
VMI: median (IQR)	39.8 (19.0-47.3)	82.0 (68.0-98.0)	<0.001	39.8 (19.0-47.3)	93.0 (72.5-99.0)	<0.001
pH: median (IQR)	7 (7-9)	6 (5-7)	<0.001	7 (7-9)	6 (5-7)	<0.001

* Wilcoxon Signed Rank test; significant level = 0.05

participants reported any serious complications at any visits.

In addition, the participants were also asked to report their levels of discomfort and pain during each treatment using the Fractional CO_2 laser. Data of each treatment were scored from 0-10 using the Visual analog scale. Friedman test was used to compared the data among all treatment sessions and found no statistically significant difference of the pain score among these three treatment sessions ($p>0.05$). Most women (>80%) had reported "not pain" and "mild pain". There were 7 and 12 women reported severe pain in the visit II and visit III, respectively. The frequency of each pain score are displayed in Table 3.

After each treatment of vulvovaginal atrophy by the Fractional CO_2 laser, participants were asked to rate their levels of satisfaction and willingness to continue the treatment by Fractional CO_2 laser. Results revealed that all participants report high level of satisfaction and none of them withdrew from the study.

Table 3. Percentage of each pain score of each laser treatments

Visit	No pain (0)	Mild pain (1-3)	Moderate pain (4-6)	Severe pain (7-10)
Visit I	40.2	54.5	5.4	0
Visit II	37.5	56.3	0	6.3
Visit III	41.1	48.2	0	10.7

Discussion

In the present study, the most bothersome VVA symptom was "feeling of dryness around vulvar" followed by the symptom of "vulvar irritation and itching". These VVA symptoms were known to be related with low level of estrogen, such as in menopausal period. The alkaline environment of the vagina, pH level >4.5, has also been used as a criteria of vaginal atrophy[11]. The average pH level of

menopausal women with VVA symptom in the present was 7.5±1.0. After laser treatment, the vaginal pH decreased significantly but no women had pH level lower than 4.5. This might be due to the gradual change of vaginal acidity and need more recovery time. Further study with longer follow-up period may help explain this finding.

Vaginal maturation index (VMI) could be used as an objective marker for vaginal atrophy. Its ratio correlates with serum FSH and E_2 level and can reveal vaginal atrophy regardless of inflammation[10,12]. The average VMI in menopausal women with VVA symptoms was 34.7±16.1%. There is no definite cut off value of VMI for diagnosis of vaginal atrophy. But the increasing ratio of VMI can use as an objective measurement to detect the recovery of vaginal epithelium. In the past, many studies could confirm the efficacy of local estrogen on vaginal epithelium by the increasing ratio of VMI. Till now, local estrogen is known to be a gold standard treatment of vulvovaginal atrophy. The present study found an estrogen like effect of Fractional CO_2 laser on the vaginal epithelium by the significant increasing of the ratio of VMI without any serious complications. For the hormonal treatment, it would be used with caution in patient with contraindication especially in hormonal sensitive cancer patient. So the Fractional CO_2 laser could be an alternative treatment that can help improve the vaginal health of the menopausal women for at least 3 months. Future studies should elucidate the long-term efficacy of Fractional CO_2 laser and whether repeated treatments are required to maintain the efficacy of this procedure.

Conclusion

Fractional CO_2 laser could be used as an alternative non-hormonal treatment for vulvovaginal atrophy with high efficacy, safety, and was easy to perform as an outpatient procedure without anesthesia. Further study needs to be done to find out its long-term efficacy, complications and the requirement of repeated treatment to maintain its efficacy especially on vaginal cytology.

What is already known on this topic?

Effect of Fractional CO_2 laser in a small group of menopausal women could improve their VVA symptoms.

What this study adds?

This study could confirm the Fractional CO_2 effect by using an objective measurement, the VMI, which may provide stronger support of the efficacy of CO_2 laser for VVA.

Potential conflicts of interest

None.

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Fractional CO_2 laser สำหรับภาวะการฝ่อแห้งของช่องคลอด

อรวรรณ เล็กสกุลไชย, กริชา ไม้เรียง, นิพัทธา วินะยะนุวัติกุล

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพระยะสั้น และความปลอดภัยของ Fractional CO_2 laser สำหรับการรักษาภาวะฝ่อแห้งของช่องคลอด*

วัสดุและวิธีการ: *จากเดือนมีนาคม พ.ศ. 2558 ถึงเดือน ตุลาคม พ.ศ. 2558 สตรีวัยทองจำนวน 112 คนเข้าร่วมการวิจัย สตรีทุกคนมีการอการฝ่อแห้งของช่องคลอดถูกรักษาด้วย Fractional CO_2 laser; พลังงาน 30 วัตต์, 1-3 ครั้ง ด้วยหัวตรวจทางช่องคลอด 360 องศา จำนวน 3 ครั้งต่อเนื่องห่างกัน 4 สัปดาห์ก่อนการรักษาด้วยเลเซอร์ การวัดอาการฝ่อแห้งของช่องคลอดแบบนามธรรมจะถูกประเมินด้วยแบบสอบถามและการวัดแบบรูปธรรมจะประเมินด้วยกระดาษค่าความเป็นกรด-ด่างและค่าอัตราส่วนของเซลบุช่อง Visual analog pain-score ถูกใช้เพื่อให้ระดับความไม่สบายตัว ระหว่างและหลังการรักษาทันทีในทุกการรักษา ที่ระยะ 3 เดือนหลังการทำเลเซอร์ครั้งสุดท้าย การวัดประเมินแบบนามธรรมและรูปธรรมจะถูกประเมินใหม่ เหตุการณ์ผิดปกติระยะสั้นและระยะยาวจะถูกบันทึก การวิเคราะห์ทางสถิติจะทำโดยใช้โปรแกรม SPSS ด้วยค่าความเชื่อมั่น p-value <0.05*

ผลการศึกษา: *ค่ากลางของคะแนนประเมินอาการฝ่อแห้งของช่องคลอดก่อนการรักษาเท่ากับ 4 และอาการที่มีผลรบกวนชีวิตมากที่สุดคือ "ความรู้สึกแห้งรอบปากช่องคลอด" มีการลดลงอย่างมีนัยสำคัญของคะแนนหลังการรักษาด้วยเลเซอร์ ค่าเปอร์เซ็นต์เฉลี่ยของ VMI ก่อนการรักษาเท่ากับ 34.7±16.1% และที่หนึ่งและสามเดือนหลังจบการรักษาด้วยเลเซอร์ ค่าเปอร์เซ็นต์เฉลี่ยของ VMI มีการเพิ่มขึ้นอย่างมีนัยสำคัญ ด้วยมีการเปลี่ยนแปลงเฉลี่ยเท่ากับ 25.0±12.2% และ 34.8±15.5% ตามลำดับ สำหรับค่าความเป็นกรด-ด่างของช่องคลอด มีค่าเฉลี่ยก่อนการรักษาเท่ากับ 7.5±1.0 และมีค่าลดลงเฉลี่ยหลังการรักษา 3 เดือนเท่ากับ 0.9±1.3 อย่างมีนัยสำคัญทางสถิติที่ค่าความเชื่อมั่น p<0.01 ไม่มีภาวะแทรกซ้อนที่ร้ายแรงและทุกคนมีความพอใจในการรักษา*

สรุป: *Fractional CO_2 laser สามารถบรรเทาอาการฝ่อแห้งของช่องคลอดและมีผลอย่างต่อเนื่องนานอย่างน้อย 3 เดือน ในการช่วยปรับปรุงสุขภาพของช่องคลอดได้อย่างปลอดภัย*