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Feasibility, Safety and Efficacy of Fractional Micro-Ablative CO_2 Vaginal ($FxCO_2$) Laser Treatment and Platelet-Rich Plasma (PRP) in Women with Urge Urinary Incontinence

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Abstract

Background: Urge urinary incontinence (UUI) is the involuntary loss of urine associated with urgency, frequency, and nocturia. Current management involves behavioural therapies, which can be time-consuming and costly to the patient, and medications, which can have side effects. Fractional micro-ablative CO2 laser (FxCO2) and platelet-rich plasma (PRP) are two novel approaches that may offer symptomatic relief for women with UUI.

Objectives: To evaluate the feasibility, safety, and efficacy of FxCO2 vaginal laser treatment and PRP in women with refractory UUI with urinary function and sexual function as secondary outcome measures.

Study Design: This was a single-centre prospective cohort study. Participants with UUI underwent three treatments of transvaginal FxCO2 laser and PRP, administered at 4–6-week intervals. Outcomes were assessed with the Australian Pelvic Floor Questionnaire (APFQ) at baseline (T1), 3-6 months (T2), and ≥12 months follow-up (T3). The 12-month follow up data were obtained by face-to-face visit or follow up telephone call. The primary outcome was change in UUI symptoms. Secondary outcomes were related to overall bladder function and sexual function. Outcomes were assessed using Wilcoxon signed-rank test.

Results: In this study, 121 participants underwent treatment with FxCO2 laser and PRP for UUI. There was a significant reduction in the average severity of all self-reported measures of primary and secondary outcomes from T1 to T2 ($p<0.02$). Improvements in all bladder function outcomes remained statistically at T3 ($p<0.04$). There were no adverse events in this cohort.

Conclusion: This study suggests that FxCO2 laser with PRP appears to be a safe, feasible, and effective treatment for UUI, bladder function, and sexual function. FxCO2 laser and PRP may have a role as an alternative therapy for severe and refractory UUI.

Keywords: Urge Urinary Incontinence; Fractional Carbon Dioxide Vaginal Laser Therapy; Platelet Rich Plasma; Bladder Function; Urinary Incontinence; Urinary Urgency

Abbreviations: UUI: Urge Urinary Incontinence; PRP: Platelet-Rich Plasma; APFQ: Australian Pelvic Floor Questionnaire; PTNS: Percutaneous Tibial Nerve Stimulation; SUI: Stress Urinary Incontinence; MUI: Mixed Urinary Incontinence; VVA: Vulvovaginal Atrophy; GSM: Genitourinary Syndrome of Menopause; OAB: Overactive Bladder.

Condensation

Combined fractional micro-ablative CO2 vaginal laser therapy and platelet-rich plasma is a safe and effective treatment of urge urinary incontinence in women with moderate to severe vaginal atrophy.

Introduction

Urge urinary incontinence (UUI) is involuntary leakage of urine accompanied or immediately preceded by urgency. Women who experience UUI may also complain of frequency and nocturia, symptoms which are attributed to detrusor muscle over activity [1]. Women suffering from troubling UUI may avoid seeking treatment due to embarrassment, misunderstanding of the cause and treatment of urinary incontinence (UI), or fear of social exclusion. Therefore, the prevalence of up to 45% of UUI in Australian women may be underestimated [2,3]. The estimated national yearly cost of UI in Australia is upwards of $1.27 billion [4]. Behavioural therapy, weight loss, pelvic floor exercises, and bladder training are first line therapy for UUI. Second line therapy includes medical treatments such as vaginal estrogen, antimuscarinics, and beta-agonists. Third line treatment includes percutaneous tibial nerve stimulation (PTNS), cystoscopic intra-detrusor injections of botulinum toxin and sacral neuromodulation [5].

The high prevalence of urinary incontinence as well as the costs and side-effects associated with current treatments has opened the door to more novel approaches [6], which include $FxCO_2$ laser and PRP.

Study Aim

This study hypothesises that women with UUI who are treated with $FxCO_2$ laser and PRP will exhibit improvements in bothersome urinary symptoms as well as other secondary outcomes.

Material and Methods

This was a prospective cohort study of women with moderate to severe UUI. They were treated with $FxCO_2$ laser (MonaLisa Touch, DEKA) and PRP (RegenLab). The Australian Pelvic Floor Questionnaire (APFQ) was used for quality-of-life assessment, which has been demonstrated to have good discriminant validity, convergent validity, and internal consistency. APFQ was completed at baseline (T1), at 3-6-month follow-up (T2), and at 12- month follow-up (T3). Subjective verbal scales were used to assess the degree of pain associated with PRP injections and laser treatment.

Participants: Inclusion criteria are patients with moderate to severe UUI with or without stress incontinence or prolapse. Exclusion criteria included urinary tract infection, current urogenital tract cancer, pregnancy, untreated cervical dysplasia, abnormal uterine bleeding, active genital herpes, and immunosuppressed patients.

Written informed consent was obtained and the study was approved by Bellberry Ethics Committee, Adelaide, South Australia, in adherence to the Declaration of Helsinki (Application ID: 2016-04-293).

Study Protocol

$FxCO_2$ laser: Participants were treated with $FxCO_2$ laser using the following settings: power 40 watts, dwell time 1,000, spacing 700, stack 3, and double pulse. Each patient received FxCO2 laser treatments with a 360-degree probe. An additional treatment with a 90° vaginal probe at the level of the bladder neck, then rotated and withdrawn in order to provide treatment of the anterior lower one-third and vestibule of the vagina as per Behnia-Willison, et al. [7-10].

Platelet-rich plasma (PRP): Patient had 10mLs of blood drawn and centrifuged on site. The PRP from the 10mLs syringe was injected to the anterior lower one-third of the vaginal subepithelial and peri-urethral areas and rolled-up 28 ×11cm PRP- impregnated gauze was inserted into vagina for 2 hours.

Treatments were delivered at intervals of four to six weeks. Patients were advised to avoid vaginal intercourse for five days after each laser application to prevent infection and pain.

Data Collection

Demographics were gathered from patients at the time of their first consultation. Data assessing aspects of UUI and related symptoms were initially gathered from patients using the APFQ and entered into an electronic medical record that was used for reference throughout the study.

Statistical Analysis

Descriptive statistics were used to describe the clinical characteristics of the patient population and study outcomes

were assessed based on responses to the APFQ at T1, T2, and T3. The responses were entered into a private database by members of the research team and later analysed using SPSS. The responses to each question at the 3 time-points were described using the median and interquartile range. Sign-rank test was used to test for differences in paired medians for each question between T1 and T2, and T1 and T3. A Bonferroni correction was applied to account for multiple comparisons, with statistical significance assessed using a 2-sided Type 1 error rate of alpha=0.002.

Results

This study involved 121 women with a mean age of 56.23 years (±14.26) and mean BMI of 27.51. Of the women, 90% (109/121) were multiparous, 71.7% (86/121) were postmenopausal, and 50% (57/114) used some variety of oestrogen treatment. Table 1 of the appendix summarises the demographics of the cohort.

Figure 1 (Appendix) shows changes in UUI symptoms. All participants experienced frequent or daily UUI symptoms at baseline. There were 89 women who were followed-up at 3 months (T2) and 58 at 12-24 months (T3). At T2, 80.9% (72 of 89) reported no or occasional UUI symptoms. These changes were also reflected in the median score reduction for UUI from pre-treatment score of 2 to post-treatment score of 1 as seen in Table 2 (Appendix). At T3 67.2% of women reported no or occasional UUI symptoms. Of the remaining 32.8%, 24.1% reported frequent and 8.6% reported daily UUI symptoms. The median post-treatment score of 1 at T2 remained the same at T3 as seen in Table 3 (Appendix).

Figure 2 (Appendix) shows 88% of the patients with moderate to severe UUI experienced symptomatic improvement, reporting 'mildly affected' or 'normal' bladder function. At T1 69.3% of women reported normal or mildly affected bladder function, with the remaining 30.7% reporting moderately and severely affected bladder function. At T2 96.4% of women reported normal or mildly affected bladder function, 3.6% reported moderately affected, and zero reported having severely affected bladder function. At T3

95.6% of women reported normal or mildly affected bladder function, 4.4% reported moderately affected bladder function, and zero reported severely affected bladder function.

There were self-reported improvements in 13 out of 15 bladder function parameters at T2 and T3 as seen in Figure 3 (Appendix).

Discussion

To the best of our knowledge, this is the first prospective cohort study to investigate $FxCO_2$ laser and PRP as a treatment for UUI in women with moderate to severe vaginal atrophy as $FxCO_2$ laser is dependent on water content of tissue. Therefore, adjuvant treatment with PRP was aimed to correct moderate to severe vaginal atrophy so that $FxCO_2$ laser can be more effective.

$FxCO_2$ laser is a potential non-surgical treatment for mild to moderate vaginal atrophy and various gynaecological conditions [7-12]. The subclinical thermal tissue effect from the laser beam induces dermal fibroblasts to initiate an inflammatory healing cascade, stimulating de novo collagen and elastin synthesis, resulting in a thicker vaginal epithelium with larger diameter, glycogen-rich epithelial cells [7-10]. There has not been a correlation found between non-ionising lasers such as those used for $FxCO_2$ laser and an increased rate of malignancy [13].

Promising results have arisen from investigations into the use of $FxCO_2$ laser in the treatment of stress urinary incontinence (SUI) [14-18], mixed urinary incontinence (MUI) [15,17], vulvovaginal atrophy (VVA) [19] genitourinary syndrome of menopause (GSM) [18, 20-26], and overactive bladder (OAB) [27]. Salvatore et al. determined $FxCO_2$ laser to be safe in remodelling tissue properties of many body regions and effective in promoting the growth of new collagen and elastic fibres [28]. They also concluded the technique to be effective in reducing symptoms of UUI in a small sample of patients with vaginal atrophy [29].

PRP treatment involves injecting autologous plasma containing concentrated platelets and growth factors to promote growth and repair damaged tissue [8,9,29-33]. PRP acts as a scaffold, stimulates angiogenesis, fibroblast synthesis, and collagen formation. Furthermore, PRP reduces healing time by 40-50% by inducing migration, proliferation and differentiation of stem cells and reducing inflammation [33]. PRP is associated with reduced treatment burden in conditions such as SUI [7,8,34,35], GSM [32], lichen sclerosus [30] and other pelvic floor disorders [9] and could be appropriate for women who are unable to use current mainstream treatment options.

Gaspar et al. noted PRP to be an effective treatment for symptoms of VVA in combination with $FxCO_2$ laser treatment through both subjective and objective measures [32]. Of the 92 participants, 40 received three $FxCO_2$ laser and PRP treatments and 52 received only PRP injections. All women continued with pelvic floor exercises. There was a significant

difference between the groups, with the former group reporting a 62.5% decrease in dyspareunia when compared to 15.4% in the latter group. The histological findings also showed a dramatic difference between the two groups, with a significant increase in the thickness of vaginal epithelium, fibroblast activity, and fibrin concentration within the cellular matrix of the former group [32].

A prospective observational study by Behnia-Willison, et al. explored $FxCO_2$ laser and PRP for the treatment of SUI in 62 women [7,8]. Each patient received three $FxCO_2$ laser and PRP treatments with 4-6-week intervals. Patient outcomes were measured using the Australian Pelvic Floor Questionnaire (APFQ) at three points in time; baseline, 3-month follow-up, and 12-month follow-up. The 3-month follow-up showed a 66% improvement in incontinence symptoms and the improvement was 62% by the 12-month follow-up suggesting a need for annual booster treatments [7].

Laser							
Author, year [Reference]	**Laser**	**Condition**	**No**	**Study type**	**Follow-up (months)**	**Assessments**	**Main findings**
Behnia-Willison, et al. [7]	Microablative fractional CO_2 laser (MonaLisa)	SUI	58	Prospective observational		APFQ	80% and 75% of patients reported improvement in SUI symptoms at 3-6 -month and 12–24-month follow-up respectively ($p<0.01$). Statistically significant improvements were seen in all secondary outcomes.
Najafian, et al. [14]	IDS Fractional CO_2 laser	SUI	55	Clinical trial		SUI severity, Visual analogue scale	Reduction of SUI severity score from 8.56±0.62 at baseline to 7.87±0.93 at 6-month follow-up ($p<0.0001$).
Menachem, et al. [15]	Ablative vaginal pixel CO_2 laser (FemiLift CO2 laser-Alma Lasers)	SUI	133	Retrospective multicentre evaluation	03-Dec	Pelvic floor distress inventory (PFDI), visual analogue scale (VAS), VVA symptoms questionnaires.	80.6% reported not using pads following treatment compared to 47.8% prior to treatment. Over 97% of patients reported no or mild urgency compared to the initial results of 7.9% and 5.3% respectively.
Fistonic, et al. [16]	Non-ablative Vaginal Erbium:Yag (Fotona)	SUI	39	Labelled, prospective, single centre pilot study	6	International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF), Q tip test, Short form 12 questionnaire (SF-12q), perineometry	Post-treatment evaluation showed significant improvement ($p< 0.05$) in all the domains tested.

Franic, et al. [17]	Fractional vaginal pixel CO_2 laser (FemiLift CO_2 laser-Alma Lasers)	SUI	85	Prospective twocentre study	6	ICIQ-UI SF, cough test, VAS.	Mean ICIQ-UI-SF score reduced from 12.0 (baseline), 7.0, (post first treatment), and 3.5 (post-second treatment) (P = 0.001). ICIQ UI SF score was 5 at 6-month follow-up. SUI symptoms were improved with 53.5% of women experiencing moderate to severe SUI symptoms at 6-month follow-up compared to 73% at baseline, 2.4% of which experienced very severe symptoms.
Perino, et al. [27]	Microablative fractional CO_2 laser (MonaLisa)	OAB	30	Prospective observational	1	VHI, VVA symptoms on VAS, micturition diary, OAB questionnaire (OAB-q)	Improvements at T1 (1 month) were seen in VVA symptoms, VHI score, micturition diary, urge episodes, and OAB-q ($p<0.0001$)
Behnia-Willison, et al. [10]	Microablative fractional CO_2 laser (MonaLisa)	GSM	102	Prospective observational		APFQ, GSM symptoms	84% of patients reported significant improvements in GSM symptoms. Secondary outcomes showed statistically significant improvement ($p>0.003$).
Sokol, et al. [26]	Microablative fractional CO_2 laser (MonaLisa)	GSM	30	Prospective observational	12	VAS for dryness, pain, itching or burning, dyspareunia, dysuria. VHIS, FSFI, SF-12q	Significant improvements were seen in VAS for all symptoms as well as in the VHI and FSFI ($p<0.001$). 92% 'satisfied' or 'very satisfied' with treatment outcomes.
Isaza, et al. [18]	Microablative fractional CO_2 laser (MonaLisa)	GSM	161	Prospective observational	36	1-h pad test, ICIQ-UI SF	Significant improvement in ICIQ-UI SF scores and 1-h pad weight test at 12 months (both $p<0.001$), 24 months (both $p<0.001$) and 36 months (both $p<0.001$). Improvements remained statistically significant at 36-month follow-up.

Athanasiou, et al. [23]	Microablative fractional CO_2 laser (MonaLisa)	GSM	94	Retrospective observational	12-Jan	VAS, ICIQ-UI SF, International Consultation on Incontinence Questionnaires-Female Urinary Tract Symptoms (ICIQ-FLUTS), Urogenital Distress Inventory-6, FSFI	There was significant improvement in symptoms severity at 1 month post final treat. Dyspareunia and dryness decreased from 9 and 8 at baseline to 0 for both symptoms (P<0.001) FSFI and frequency of sexual intercourse increased from 10.8 and 1 at baseline to 27.8 and 4 (P<0.001). These benefits remained unchanged at 12-month follow-up.
Paraiso, et al. [24]	Microablative fractional CO_2 laser (MonaLisa) vs vaginal oestriol cream	GSM	69	RCT	6	VAS vaginal dryness score, patient global impression of improvement (PGI-I)	As per PGI-I, 85.8% of laser participants rated their improvement as "better or much better" and 78.5% reported being either "satisfied or very satisfied" compared to 70% and 73.3% in the estrogen group.
Pitsouni, et al. [22]	Microablative fractional CO_2 laser (MonaLisa)	GSM	53	Prospective observational	3	VHI, FSFI,vaginal maturity value (VMV),ICIQ-FLUTS, ICIQ-UI SF, Urogenital Distress Inventory (UDI-6), King's Health Questionnaire (KHQ).	VMV, VHIS, and FSFI increased significantly. Significant improvement was seen in symptoms of dyspareunia, dryness, burning, itching, dysuria, frequency, urgency, urgency incontinence, stress incontinence and scores on the ICIQ-FLUTS, ICIQ-UI SF, UDI-6 and KHQ at 3 -month follow up.
Cruz, et al. [19]	Microablative fractional CO_2 laser (MonaLisa) vs vaginal oestriol vs Microablative fractional CO_2 laser (MonaLisa) and vaginal oestriol	VVA	45	RCT	5	Vaginal health index (VHI), VAS, female sexual function index (FSFI)	Significant improvements were seen in VHI in all study groups (laser, vaginal oestriol, and laser with vaginal oestriol). Improvements in dryness, dyspareunia, and burning were seen in laser plus oestriol and laser only (p<0.009). Laser plus oestriol had significant improvement in FSFI score (p<0.004).

Salvatore, et al. [28]	Microablative fractional CO_2 laser (MonaLisa)	VVA, vaginal laxity, UI	38	Prospective observational	1	VAS for dryness, vaginal laxity, itching or burning, and dyspareunia, histological examination	Reduction in mean VAS values for dysuria (1.3 to 0.4), urinary urgency (2.6 to 0.8), UI (1.6 to 0.7), and SUI (3.1 to 1.3) at baseline and after 3 sessions respectively. Histology showed growth of new collagen and elastic fibres.
Salvatore, et al. [29]	Microablative fractional CO_2 laser (MonaLisa)	VVA	50	Prospective observational	3	FSFI, SF-12q	VVA symptoms -vaginal dryness, vaginal burning, vaginal itching, dyspareunia, dysuria-improved at 12-week follow-up $p < 0.001$). VHIS increased from 13.1± 2.5 (baseline) to. 23.1 ± 1.9 (12-week follow-up) ($p < 0.001$). Significant improvement in quality of life($p<0.001$).
PRP							
Author, year [Reference]	**Combined therapy**	**Condition**	**No**	**Study type**	**Follow-up (months)**	**Assessments**	**Main findings**
Behnia-Willison, et al. [30]	Nil	Lichen Sclerosus	28	Prospective observational	Dec-24	Verbal interview on symptom severity, colposcopy	On colposcopy at 12 months, lesions were not seen in 8, lesions were smaller in 17, and lesions were the same in 3 women. 15 women experienced no associated symptoms and 13 had intermittent symptoms including itch, pain, dyspareunia.
Laser and PRP							
Author, year [Reference]	**Laser**	**Condition**	**No**	**Study type**	**Follow-up (months)**	**Assessments**	**Main findings**
Behnia-Willison, et al. [8]	Microablative fractional CO_2 laser (MonaLisa)	SUI	62	Prospective observational	Dec-24	APFQ	66% (41/62) women reported improved SUI symptoms at 3–6-month follow-up ($p<0.001$). Of the women reached for 12-month follow-up, 62% (23/37) reported maintained improvements in SUI symptoms.
Gaspar, et al. [32]	Microablative fractional CO_2 laser (MonaLisa)	VVA	92	Case control	3	Sexual health, histology	Decreased discomfort during sex and improvement in vaginal mucous histology.

Table 1: Summary of the critical literature survey for the specific application of PRP and $FxCO_2$ laser in conditions such as SUI, GSM, VVA and UI.

This study suggests that $FxCO_2$ laser is a potential beneficial treatment for UUI and related bladder issues in women. Following treatment with $FxCO_2$ laser and PRP, patients reported short-term improvements in self-reported measures of bladder function, urge incontinence, frequency, nocturia, urgency, pad use, UTI, daily activities effects, bothersome bladder problems, and limiting fluid. All symptom improvements remained statistically significant at the long-term (≥12-month) follow-up. These findings emerge in the context of a need for alternatives to conventional treatments for UUI, which may be costly, have side effects, and be sometimes unsuitable for patients. As UUI affects up 45% of women [1], it is important that patients are provided with options. A trend towards re-emergence of some symptoms at ≥12-month follow–up suggests the need for a booster treatment to maintain long-term symptomatic relief. The timing of a booster treatment depends on the aging process and menopause status. Interestingly, all improvements remained statistically significant at T3. Although vaginal estrogen was offered to all the women with vaginal atrophy only 50% of the cohort were compliant. Vaginal estrogen appears to maintain the symptom control in the group with improved urinary symptoms as seen at Cruz, et al. [19]. A study limitation was the attrition rate during COVID pandemic, with half of the women participating in the ≥12-month face-to-face follow-up, making it difficult to form comparisons from baseline to the final follow-up. However, through teleconsultations many of women who did not return for 12-month follow-up were found to have symptom resolution and successful conservative management measures. Secondly, symptom improvements following PRP treatment might be due to the tissue needling involved in the injection process, rather than to the bio-regenerative effects of the PRP. Subjecting tissue to micro-trauma may instigate the tissue repair cascade [36], and in the present circumstances, this cannot be ruled out as a confounding factor. Future studies should attempt to control for these potential treatment mechanisms in their design, which would include a placebo PRP and sham arm of laser therapy.

Conclusion

$FxCO_2$ laser and PRP may improve UUI, sexual function, and overall bladder function. These treatments appear to be safe, tolerable, and have minimal downtime as they can resume their normal daily activities immediately after treatment with the exception of abstinence for three days. The treatment effects may diminish significantly by 12-18 months and may require a booster treatment to maintain symptom relief. Further randomised control trials are warranted to confirm the efficacy of these treatment modalities for UUI.

Disclosures

The authors have no conflict of interest and have not received any direct support (financial or otherwise) to conduct this study.

Conflicts of Interest

Dr Behnia-Willison worked as a consultant for Regenlab® for 6 months in 2018. The other authors have no conflict of interest and have not received any support (financial or otherwise) to conduct this study.

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