The first published randomised controlled trial of laser treatment for vaginal atrophy raises serious questions

We still await well conducted RCTs of CO_2 laser therapy for vaginal atrophy; in the meantime, topical oestrogen therapy remains the gold standard

Vaginal laser therapy has entered the global marketplace promising women relief from symptoms of genitourinary syndrome of menopause (GSM), formerly known as vulvovaginal atrophy.

Current accepted treatments for GSM include topical oestrogens, which have demonstrated subjective and objective symptom improvement in more than 80% of patients in randomised controlled trials (RCTs) but require regular use, usually twice weekly. Compliance can therefore be an issue, and some patients, particularly those who have been treated for breast cancer, may have safety concerns.

Some laser treatment devices have received clearance in the United States by the Food and Drug Administration (FDA), but not specifically for the treatment of GSM. The lack of properly controlled trials led the American College of Obstetricians and Gynecologists to publish a statement of warning to its members in May 2016.[1] In July 2018, the FDA released a press statement on efforts they were taking to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for "vaginal rejuvenation" (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm615130.htm).

In Australia, the Therapeutics Goods Administration has similarly approved CO_2 laser therapy for "incision, excision, vaporization and coagulation of body soft tissues using carbon dioxide as the substrate. Its typical applications are oral surgery, dermatology, ENT and gynaecology". CO_2 laser therapy is not specifically listed for treatment of GSM.[2]

It is uncertain how many laser treatments for symptoms of GSM are being performed in Australia, as episodes of treatment cannot be tracked by a specific Medical Benefits Schedule item number. Currently, treatments are being offered in specialist, general practice and cosmetic medicine settings. Many internet advertisements in Australia are marketing laser therapy as a treatment for symptoms (itch, dryness, pain, urinary incontinence, prolapse) rather than diagnosed conditions, without rigorous data to support the assertions that it is efficacious. Patients using the internet for information about treatments may be from vulnerable populations unable to critically analyse the rigour of published data. Moreover, some of the individuals offering laser therapy may not have the expertise to diagnose the conditions responsible for the patient's symptoms.

These treatments are significantly more expensive than topical vaginal oestrogens, and patients risk financial harm if they expend funds on non-efficacious treatments. However, if the treatment does work, then patients who feel unable to use topical vaginal oestrogen therapy (breast cancer survivors) need to have confidence that laser is effective.

It is important to note that companies promoting vaginal laser treatment do not currently need to provide evidence from stringently conducted phase 3 clinical trials in order to receive device clearance in the US or Australia, whereas well conducted placebo-controlled RCTs are essential for the registration of pharmaceuticals. The FDA has published guidelines for the conduct of trials of pharmaceutical treatments for GSM.[3] These guidelines set out the endpoints that should be studied, including objective assessment of vaginal health by measures such as vaginal pH and the vaginal maturation index, which assesses the percentage of parabasal, intermediate and superficial vaginal cells on a vaginal smear. They suggest that information be obtained regarding the patient's subjective symptoms; for instance, the most bothersome symptom. Moreover, it is important to note that placebo effects of 30–41% on various outcome measures have been observed in stringently controlled pharmaceutical trials.[4,5]

The published data until recently consist of uncontrolled case series.[6-12] The first RCT, conducted by Cruz and colleagues, was reported in early 2018.[13] The abstract and conclusions of this trial might suggest that vaginal laser therapy has a place in the treatment of GSM. However, a careful reading of the paper raises many questions.

The RCT[13] compared CO_2 laser/placebo cream, sham laser/oestrogen cream and CO_2 laser/oestrogen cream. It was a very small trial, with 15 patients in each arm, and much of the data fail to reach statistical significance. Methodological concerns with the trial include:

- The placebo effect was not properly evaluated, as the trial lacked a sham laser/sham cream arm.
- The Vaginal Health Index (VHI) score used was a cumulative score recording vaginal elasticity, fluid volume, moisture, epithelial integrity and vaginal pH, and the first four parameters were subjective and therefore open to assessor bias. The authors did not independently report vaginal pH, the only objective measure in the VHI.
- There is a disparity between the outcomes reported in the trial and those listed to be evaluated in the trial registration (https://clinicaltrials.gov/ct2/show/NCT02419729). At trial registration, the authors stated that they would administer both the International Consultation on Incontinence Questionnaire Short Form and the Menopause-Specific Quality of Life

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Questionnaire and compare vaginal biopsies before treatment and at 17 weeks, none of which were reported.

- There is a disparity between the results reported and the authors' conclusion that CO_2 laser alone or in combination with topical oestrogen is a "good treatment option". However, the trial found that the vaginal oestrogen intervention had a significantly higher VHI score (better outcome) and lower rate of dyspareunia on the validated self-administered Female Sexual Function Index compared with the CO_2 laser/sham oestrogen cream arm. The patients in the laser/sham cream arm reported a significant worsening of pain after treatment, without any differences being detected between the groups on the remaining outcomes. Additionally, the authors cited six references reporting dyspareunia as a side effect of fractional CO_2 laser. Based on the trial results, the correct conclusion should have been that vaginal oestrogen therapy is the preferred treatment for GSM.
- The authors failed to discuss the important patient cost differential between CO_2 laser treatment and topical vaginal oestrogen therapy.

Despite the publication of this first RCT, it remains the case that RCTs of vaginal laser treatment for GSM with a true placebo arm are urgently needed. Meanwhile, clinicians should remain cognisant of the fact that vaginal laser therapy as administered in this trial worsened pain, and that topical vaginal oestrogen therapy remains the gold standard.

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