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SHORT REPORT

Safety of vaginal erbium laser: A review of 113,000 patients treated in the past 8 years

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ABSTRACT

Background: Energy-based devices are becoming a popular option for minimally invasive vaginal procedures. The aim of this study was to obtain information on the frequency of occurrence of adverse effects (AEs) related to vaginal erbium laser (VEL™) treatment.

Materials and methods: The global survey was conducted among practitioners using the non-ablative VEL™ (Fotona, Ljubljana, Slovenia). Users were invited to provide the number of patients treated with VEL™ and the number of observed laser-related AEs.

Results: The survey was conducted from August 2018 to April 2019. Responses from 535 practitioners were collected, with a total of 113,174 patients treated in the period from 2012 to 2019. Out of 535 respondents, 160 (30%) shared detailed information about the indications they treated in a population of 62,727 patients, whereas 188 (35%) respondents provided information on the frequency of AEs observed in their treated population of 43,095 patients. All observed AEs were mild to moderate, transient and appeared with low frequencies.

Conclusions: Minimally invasive thermal-only laser treatment using the non-ablative VEL™ procedures appears to be safe and the incidence of AEs is low.

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Introduction

In the last decade, there has been an ever-growing user demand for minimally invasive procedures for treating symptoms of pelvic floor dysfunction. Some of the most promising treatments were developed using energy-based devices, such as lasers (Erbium:YAG and CO_2) and radiofrequency. The FotonaSMOOTH® non-ablative thermal-only Er:YAG technology[1] (Fotona, Ljubljana, Slovenia) has been specially developed for minimally invasive intravaginal treatments. Four different treatment protocols that incorporate non-ablative thermal-only Er:YAG technology have been developed and clinically validated for the following indications: stress urinary incontinence (SUI)[2], vaginal laxity/vaginal relaxation syndrome[3], genitourinary syndrome of menopause (GSM)/vulvovaginal atrophy (VVA)[4], and pelvic organ prolapse (POP)[5]. The non-ablative thermal-only Er:YAG technology works by creating rapid sequential heat pulses that are transferred deeper into mucosa (up to 500 μm), without overheating the tissue surface. As a result of this precisely controlled heating, the temperature in the vaginal wall increases to approximately 65 °C, the optimal temperature that allows the shortening of the collagen fibrils without irreversible denaturation of their structure[6]. Shortening of the collagen fibrils leads to contraction and shortening of the irradiated mucosal tissue. Tissue exposure to the increased temperature has an additional longer-lasting effect through stimulation of remodeling of the existing collagen and generation of new collagen (neocollagenesis)[7]. The first-generation laser technology used to treat genitourinary problems was microablative fractional CO_2 laser that works by creating superficial microablation zones on the mucosal tissue. This triggers a healing response and formation of new collagen. Similar effects of skin renewal and collagen formation following rapid wound healing have been described also with the use of microablative fractional Er:YAG laser.

In contrast to ablative procedures, the non-ablative procedure produces pulsed heating of the vaginal wall and induces remodeling of epithelial and connective tissues without causing epithelial injury[8]. With the non-ablative thermal-only Er:YAG technology, the tissue surface remains intact, and the risk of unwanted adverse effects, especially after multiple repeated treatments, is greatly reduced.

In the Food and Drug Administration (FDA)'s Safety Communication[9] that was made public in 2018, the FDA questioned the safety of these procedures, mentioned the lack of clinical data[9], and highlighted the need for further clinical evidence, which has been previously stressed also by several editorials and review papers addressing the use of energy-based devices, including VEL™, in the field of gynecology and urogynecology[10–13]. Several manufacturers of energy-based devices also received the FDA warning letter

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about inappropriate marketing of their devices for 'vaginal rejuvenation' procedures in the USA.

There are different methods for safety assessment of any medicinal product or medical device. One of the methods is the obligation of manufacturers and is called post-market surveillance (PMS). PMS encompasses various activities of active monitoring of the products that have been put on the market (analogous to pharmacovigilance procedures for pharmaceuticals). It is legally binding and requires reporting to national and international regulatory bodies. Another way to assess the safety of new procedures is through active involvement of the concerned scientific community. It involves addressing initiatives to policy makers and encouraging and enabling the community members to perform clinical research activities. In the light of active participation, the Vaginal Erbium Laser™ Academy (VELA) was established. VELA is an independent scientific organization devoted to women's health and quality of life by developing and implementing the innovative VEL™ non-ablative thermal-only Er:YAG technology. The organization receives sponsorship from Fotona (the manufacturer of the laser systems) for organization of the yearly VELA Symposium.

VELA has initiated this international survey in order to evaluate the clinical indications for use of VEL™ technology in practice and to analyze the occurrence of VEL™-related adverse effects (AEs) in clinical practice.

Materials and methods

The survey was sent to the VEL™ end-users through the existing network of VELA members, Fotona's international distributors and the Fotona Clinical Affairs (CA) Department. It included a simple request to provide the number of patients that were treated and the number of laser-related AEs observed in their practice during a specified (active) period from 2012 to 2019. The survey was prepared in an electronic table form which included a list of all known AEs related to laser treatment.

Data collection took place from August 2018 to April 2019. Data analyses on pooled data were performed using SPSS statistical software (Version 23, IBM Corp., Chicago, USA).

The following metrics were calculated/reported:

- The total number of users who responded to the survey,
- The global distribution of users,
- The total number of treated patients in a defined time period for each VEL™ application ('patient population structure'),
- Global patient population structure and structure by geographical region,
- A list and frequencies of all observed AEs,
- Overall frequency of observed AEs, calculated per total population of patients from the sites that provided information on AEs (respondents included in the safety analysis).

The bootstrapping method for calculating confidence intervals was employed to compensate for the uncertainty of the normality of the data distribution and small sample sizes of some observed AEs. The main reason for using the bias-corrected and accelerated (BCa) bootstrap interval is that it corrects for bias and skewness in the distribution of bootstrap estimates. The calculated BCa intervals in this study represent 95% confidence intervals (95% CI) of observed AE frequencies.

Respondents who provided information about AEs in a descriptive, qualitative manner (verbatim, for example: 'rare side-effects, spotting, discharge, *de novo* incontinence' or 'minimal pain, feeling of edema, little spotting') were deemed unsuitable for further consideration in the safety analysis. The nature of such information does not allow quantitative analysis. Their responses were nevertheless screened for a signal of any new, previously undescribed AE.

Results

A total of 535 practitioners from 43 different countries responded to the survey and reported about 113,174 patients being treated during the period from 2012 to 2019 (Table 1). Out of 535 respondents, 160 (30%) provided detailed information on their patient population structure by treated indication. These sites included 62,727 patients, which represent 55% of all patients whose data were gathered by this survey. According to data from these respondents, 46% of the patients received treatment for vaginal laxity, 31% were patients with SUI, 9% suffered from GSM, 7% had POP, while 7% of the patients had concurrent symptoms of vaginal laxity and SUI.

Thirty-three out of 535 respondents (6.2%) provided only qualitative, descriptive information about AEs observed in their practices; 188 out of 535 respondents (35%) provided quantitative data on AEs observed in their clinical practice (Figure 1).

The analysis of AEs was performed on the data from sites reporting quantitative data on AEs ($n = 188$, 35% of all

Table 1. Overview of the collected data presented by geographical region.

Region/country	*Total number of sites*	*Total number of patients*	*Number of sites reporting on adverse effects*	*Number of patients from adverse effect-observant sites*
Asia	209	71,159	76	27,452
Australia	8	418	6	269
Europe	88	9,687	20	2,515
Middle East	109	20,800	79	11,642
North America	84	2,683	6	667
South America	37	8,427	1	550
Total	535	113,174	188	43,095

respondents). Table 1 shows the cumulative number of patients treated at these sites ($n = 43,095$) and their regional distribution; 43,095 patients from these sites represent 38% of all patients whose data were gathered by this survey.

Table 2 reports the AEs observed in different sites, with different frequencies. Overall frequency is reported as a quotient of the absolute number of AE occurrences (data not shown) and the total number of patients included in the safety analysis ($n = 43,095$).

The BCa bootstrap interval represents the 95% CI of the mean of the reported frequencies of AEs (Table 2).

There were no new, previously unobserved and unreported AEs recorded at sites that provided qualitative and descriptive information only. There have been two reports of abnormal bleeding following the laser treatment, but the source of abnormal bleeding (e.g. menstrual bleeding or mucosal injury) has not been provided.

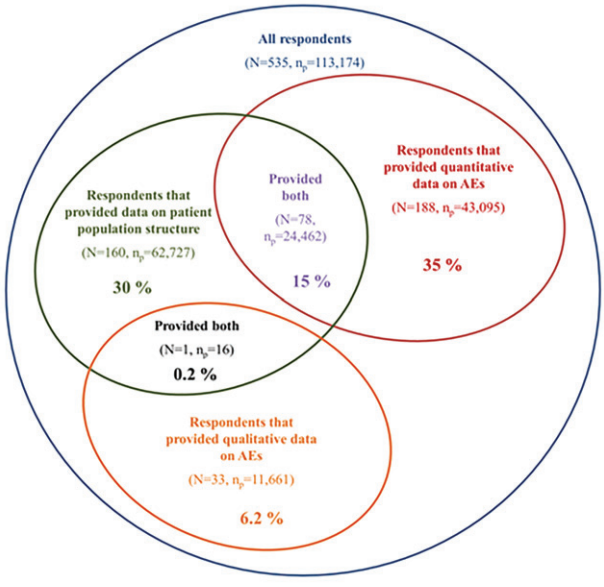

Figure 1. Venn diagram showing proportion of respondents providing qualitative or quantitative data or both on adverse effects reported in their clinical practices.

Discussion

To our knowledge, this study reports the largest survey on the frequency of AEs for any procedures performed in gynecology based on energy-based devices.

The results on safety were obtained from the data of a portion of the participants (188 respondents, 35%). The remaining respondents did not provide quantitative evaluation of the AEs observed in VEL^{TM}-treated women. The majority of the AEs have already been observed and reported in published research papers which described the use of VEL^{TM}. They have been recognized by the manufacturer and are regularly evaluated. We have observed high variability in the reported frequencies of AEs. There are several possible explanations for this; first, some of the observed AEs, as in the case of edema and vaginal discharge, are not considered problematic in terms of severity, and are not even considered as an AE by all practitioners. Edema is more commonly regarded as an indicator of the thermal effect of the VEL^{TM} application, and is therefore considered an anticipated treatment response. Vaginal discharge, described as watery, is an indicator of edema resolution. Furthermore, assessment of AEs depends on the organizational set-up and follow-up routine of each clinical practice. An important factor that needs to be considered is the patients' informed consent process; if the process is adequate, the patients are informed about possible AEs that may occur, are able to make self-assessment after the procedure and consider whether a particular AE is worth reporting. The practitioner's experience and patient selection are also factors to be considered.

When comparing the overall frequencies of AEs collected by this survey with the frequencies of AEs reported in the published studies where VEL^{TM} technology was used for the same indications (pooled data of 19 trials with a total of 1,570 patients from Fotona data on file), a high consistency of the results was observed. The frequency of occurrence of burns, which are a result of overtreatment and can be considered a result of laser misuse, is very low, and these have been reported by only seven (of 188; 3.7%) respondents. The occurrence could most probably be attributed to the practitioner's learning curve. There have been two reports of

Table 2. Reported adverse effects (AEs), mean frequency of AE occurrence, range of reported frequencies, and calculated overall frequency.

Adverse effect	*Number of respondents reporting the AE (n)*	*Mean of frequencies (%)*	*Range of frequencies (%)*	*BCa bootstrap interval*[a]	*Overall frequency (%)*[b]
Vaginal discharge	47	6.53	0.00–100	3.69–9.67	4.01
Edema	23	3.72	0.00–100	1.80–5.86	3.45
Pain (during treatment)	30	1.92	0.00–50.0	1.09–2.92	1.44
Pinpoint bleeding	33	1.55	0.00–50.0	0.87–2.36	1.16
Dryness	14	0.22	0.00–7.37	0.10–0.36	0.48
De novo urinary incontinence	13	0.28	0.00–14.3	0.12–0.49	0.21
Burns	7	0.10	0.00–10.0	0.02–0.22	0.16
Post-operative pain	7	0.47	0.00–37.7	0.07–1.06	0.10
Mild irritation of the introitus	4	0.56	0.00–70.0	0.007–1.70	0.44
Discoloration	2	0.10	0.00–16.7	0.003–0.32	0.02
Itching	2	0.06	0.00–10.0	0.001–0.24	0.01
Infection	4	0.03	0.00–3.33	0.001–0.07	0.01
Abnormal bleeding	1	0.04	0.00–6.67	0.04–0.16	0.005
Dyspareunia	1	0.004	0.00–0.69	0.04–0.17	0.002

[a]BCa, bias-corrected and accelerated (BCa) bootstrap interval, based on 1000 bootstrap samples (999 for burns, 982 for introital irritation, 985 for infection, 866 for itching, 653 for abnormal bleeding, 637 for dyspareunia, 858 for discoloration); [b]calculated as the number of AEs per patients included in the safety analysis ($n = 43,095$).

abnormal bleeding following the laser treatment, but the source of abnormal bleeding (e.g. menstrual bleeding or mucosal injury) has not been established. Unfortunately, neither the age nor hormonal status of these patients is known. Abnormal and irregular bleeding is quite common in perimenopausal women, which makes establishing of the cause and effect quite difficult.

AEs that may occur because of laser misuse emphasize the need for well-structured and standardized training on appropriate laser (or any energy-based device) handling. Many manufacturers already provide their users with training workshops, but whether this is an established practice in the whole of the energy-based device industry remains to be answered. As the use of these devices become widespread in clinical practice, the introduction of such training to continuing medical education will be necessary. In fact, VELA already provides continuous medical education and encourages experience and data-sharing among the VEL^{TM} users.

The observed and reported AEs by respondents to this global survey were graded as mild or moderate, they were transient in nature and their frequency of occurrence was low. The main advantage of surveys such as the present one, as well as registry trials, is that the large number of included patients provides a realistic representation of everyday clinical practice[14]. Although clinical trials provide information about possible AEs, they usually do not last long enough to detect AEs that take a long time to develop and usually do not include enough patients to detect rare AEs. Furthermore, clinical studies usually have stringent inclusion criteria, meaning that the results cannot always be generalized. In our opinion, the significant period of time (8 years) of active VEL^{TM} use in clinical practice and the number of women included in the survey make this survey a relevant resource on VEL^{TM} use and safety. Clearly, there are other energy-based devices that are being used in the field of gynecology for the same or similar indications, but, since they utilize different technologies for delivering energy to the target tissue, the results of this survey cannot and should not be extrapolated to other energy-based devices.

This study has certain limitations. The response rate among VEL^{TM} users is relatively low (35%). This could have resulted in non-response bias. In addition, the lack of demographic data prevented us making a more accurate evaluation of AEs; the AEs provided by the respondents are self-reported and some users have been collecting them for a longer period of time, rendering the data historical and more prone to inaccuracies.

These limitations should be remedied in the future by introducing well-designed, regularly evaluated registries, where the users would log every treatment using any of the energy-based devices and record the outcomes, side-effects or AEs, as well as complications and patients' satisfaction. A prospective VELA study has been designed in order to collect basic information of patients submitted to different VEL treatments[15]. The main aim of the VEL^{TM} Academy is to establish and improve the management of a well-defined registry by introducing a web-based program to ease VELA members' contribution with the data from their everyday clinical practice.

Conclusions

The VEL^{TM} appears to be safe for surveyed indications and carries a very low risk profile. The reported adverse effects were mild to moderate, transient in nature and occurred with very low frequencies. The use of well-designed registries with long-term follow-up, such as that used by VELA, should be encouraged to evaluate clinical indications and the frequency and severity of adverse effects.

Potential conflict of interest Neža Koron and Zdenko Vizintin are employees of Fotona d.o.o., manufacturer of the medical device used in the study. No potential conflict of interest was reported by other authors.

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