



Effects of titanium dioxide microcrystals with covalently bonded silver ions and Aloe Vera extract (TIAGIN®) on the Vaginal Health Index Score (VHIS) and Female Sexual Function Index (FSFI) in patients with vaginal de-epithelialization: a prospective, single-center cohort analysis

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ABSTRACT

Objective: to evaluate the effects of titanium dioxide microcrystals with covalently bonded silver ions and Aloe Vera extract (TIAGIN®) on the Vaginal Health Index Score (VHIS) and Female Sexual Function Index (FSFI) in patients with vaginal de-epithelialization.

Materials and methods: we enrolled 45 post-menopausal women with vaginal de-epithelialization, who underwent VHIS evaluation and completed an FSFI test. We recorded their age, age at onset of menopause, parity and Body Mass Index. After this baseline evaluation, patients underwent 30 days of vaginal treatment with one capsule per day of TIAGIN®. After treatment, all patients were evaluated again using the same methods as the pre-treatment phase.

Results: after treatment there was significant improvement in all VHIS parameters (elasticity, fluid secretion type and consistency, pH, epithelialization of vaginal mucosa, and moisture) and in the total score ($p=0.006$). Similarly, after treatment there was also a significant improvement in 4 FSFI areas (lubrication, orgasm, satisfaction, and pain) and in the total score ($p=0.005$). None of the patients reported any local or systemic side effects during treatment.

Conclusions: we observed a significant improvement in both the VHIS and FSFI, which can be considered direct and indirect signs of increased vaginal epithelialization following vaginal treatment with TIAGIN®.

Keywords: Aloe Vera, silver ions, Vaginal Health Index Score, Female Sexual Function Index (FSFI), vaginal de-epithelialization.

SOMMARIO

Obiettivo: valutare gli effetti di microcristalli di biossido di titanio con ioni d'argento covalentemente legati ed estratti di Aloe Barbadensis (TIAGIN®) sul Vaginal Health Index Score (VHIS) e Female Sexual Function Index (FSFI) in pazienti affette da disepitelizzazione vaginale.

Materiali e metodi: abbiamo arruolato 45 donne in post-menopausa affette da disepitelizzazione vaginale, valutate mediante VHIS e FSFI. Abbiamo registrato età, età di insorgenza della menopausa, parità e Body Mass Index. Dopo la valutazione iniziale, le pazienti sono state trattate con una capsula vaginale al giorno di TIAGIN®, per 30 giorni. Dopo il trattamento, tutte le pazienti sono state rivalutate usando la stessa metodologia applicata durante la valutazione iniziale pre-trattamento.

Risultati: dopo il trattamento abbiamo osservato un miglioramento significativo di tutti i parametri del VHIS (elasticità, tipo e consistenza della secrezione, pH, epitelizzazione e umidificazione della mucosa vaginale) e dello score totale ($p=0.006$). Parallelamente, abbiamo osservato anche un miglioramento di 4 domini del FSFI (lubrificazione, orgasmo, soddisfazione, dolore) e dello score totale ($p=0.005$). Nessuna delle pazienti ha riportato effetti indesiderati locali o sistemici durante il trattamento.

Conclusioni: i nostri dati dimostrano significativi miglioramenti sia del VHIS che del FSFI, che possono essere considerati segni indiretti dell'aumentata epitelizzazione vaginale dopo trattamento con TIAGIN®.

INTRODUCTION

There is mounting evidence to suggest that sexual health plays a pivotal role throughout women's lives, from puberty to the post-menopausal period^(1,2). According to the World Health Organization, sexual health requires a positive approach to human sexuality and an understanding of the complex factors that shape human sexual behavior⁽³⁾. Despite the need for more epidemiological research into female sexual dysfunction (FSD), it is widely acknowledged that it increases as women age and affects about 40-45% of adult women⁽⁴⁾. To this regard, common risk factor categories associated with FSD include individual general state of health, diabetes mellitus, cardiovascular disease, other genitourinary diseases, psychiatric/psychological disorders, other chronic diseases, and socio-demographic conditions⁽⁵⁻⁸⁾. Nevertheless, the multidimensional nature of human sexuality may also play a detrimental part in objectifying the real contributing factors to possible dysfunctions^(9,10).

On the basis of these elements, several approaches and methods have already been proposed in order to recognize and measure sexual health, FSD rate, and severity. As has been widely reviewed by Rosen⁽¹¹⁾, on one hand objective measures, such as vaginal photoplethysmography or Duplex ultrasound, have been used in some studies but lack standardization and are unsuitable for use in large-scale clinical trials, while on the other hand, self-reported event logs or questionnaires are best suited for research or clinical assessment of female sexual function. Among these questionnaires, one of most used and validated is the Female Sexual Function Index (FSFI)⁽¹²⁾, which consists of 19 items designed to assess 6 important areas of female sexuality: desire, arousal, lubrication, orgasm, satisfaction, and pain. In addition to these important determining factors, numerous studies have reported that adequate vaginal epithelialization is strictly related to satisfactory quantity and quality of sexual activity⁽¹³⁾, even after autologous in vitro cultured vaginal tissue transplantation in patients with Meyer-von-Rokitansky-Küster-Hauser syndrome^(14,15). Like the FSFI, the need for an objective and measurable evaluation of vaginal mucosa led to the development of the Vaginal Health Index Score (VHIS)⁽¹⁶⁾, which analyzes overall elasticity, fluid secretion type and consistency, pH, epithelialization of vaginal mucosa, and moisture.

Several pharmacological treatments have already been developed to improve vaginal

epithelialization and, consequently, sexual health in the female population^(17,18). Nevertheless, current data is still not sufficient to draw any firm conclusions regarding the gold standard treatment. Recent evidence reported that Aloe Vera extracts have significant antioxidant⁽¹⁹⁾, antibacterial⁽²⁰⁾, anti-inflammatory, and wound-healing properties⁽²¹⁾. Furthermore, similar beneficial properties were reported for silver ions⁽²²⁻²⁴⁾.

Considering these elements and the lack of robust available data in literature, the aim of the current study is to evaluate the effects of titanium dioxide microcrystals with covalently bonded silver ions and Aloe Vera extract (TIAGIN®) on the VHIS and FSFI in patients with vaginal de-epithelialization.

MATERIALS AND METHODS

We performed a prospective, single-center cohort analysis between March and May 2016 at the Gynecology and Obstetrics Unit, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina (Messina, Italy). We enrolled post-menopausal women with vaginal de-epithelialization, excluding patients with significant comorbidities (chronic cardiovascular, immune, endocrine, and metabolic disorders, and cancers) and patients who had used any other kind of pharmacological treatment (including the substances tested in this study) during the previous 3 months.

The study design complies with the Declaration of Helsinki, conforms to the Committee on Publication Ethics (COPE) guidelines (<http://publicationethics.org>), and was approved by the Institutional Review Board (IRB) of the hospital where it was performed. Each patient who participated in this study was fully informed of the procedures involved and signed a consent form for data collection for research purposes.

All the design, analysis, data interpretation, drafting, and revision processes complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies⁽²⁵⁾, available through the EQUATOR (Enhancing the QUALity and Transparency Of health Research) network (<http://www.equator-network.org>).

For all the enrolled patients, we recorded age, age at onset of menopause, parity, and Body Mass Index (BMI). All the patients underwent VHIS

evaluation (as described by Bachmann et al.)⁽¹⁶⁾, always performed by the same gynecologist in order to avoid inter-observer variability, and completed the FSFI test.

After this baseline evaluation, all the enrolled patients underwent 30 days of vaginal treatment with one capsule per day of titanium dioxide microcrystals with covalently bonded silver ions and Aloe Vera extract (TIAGIN®). Any patient taking less than 80% of the allocated dose of study drug was regarded as noncompliant and excluded from the study. The study drug was supplied free of charge and none of the enrolled patients were paid to join or continue the study.

After treatment, all the patients were evaluated again using the same methods as the pre-treatment phase (VHIS evaluation by the same gynecologist who performed it during the pre-treatment phase and self-reported FSFI). All the side effects were recorded and an independent data safety and monitoring committee evaluated the study results.

Statistical analyses were performed by using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) software package. The assumption of normal distribution for continuous variables was tested with the Kolmogorov-Smirnov test for goodness of fit. Continuous variables were compared between pre- and post-treatment phases using the Student t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

We enrolled 45 patients who met the inclusion/exclusion criteria and signed an informed consent form. Age, age at onset of menopause, parity, and BMI are reported in **Table 1**. All the patients declared that they took at least 90% of the allocated dose of study drug (good compliance).

Table 1.
Characteristics of enrolled patients

	Mean ± Standard Deviation
Age	56.9 ± 10.0
Age of menopause onset	48.8 ± 2.9
Parity	2.3 ± 0.8
Body Mass Index	23.8 ± 3.2

Pre- and post-treatment VHIS results are reported in **Table 2**, whereas results for FSFI are reported in **Table 3**. In particular, after treatment there was a significant improvement in all VHIS parameters (elasticity, fluid secretion type and consistency, pH, epithelialization of vaginal mucosa, and moisture) and in the total score (p=0.006). Similarly, after the treatment there was also a significant improvement in 4 FSFI areas (lubrication, orgasm, satisfaction, and pain) and in the total score (p=0.005), whereas the improvement for the remaining 2 areas (desire, arousal) was not significant (p=0.126 and p=0.082, respectively). None of the patients reported any local or systemic side effects during treatment.

Table 2.
Comparison of Vaginal Health Index Score between pre-treatment and post-treatment phases.

Vaginal Health Index parameters	Pre-treatment (Mean ± Standard Deviation)	Post-treatment (Mean ± Standard Deviation)	p
Elasticity	2.4 ± 0.8	2.7 ± 0.5	0.036
Fluid Secretion type and consistency	2.0 ± 0.8	2.3 ± 0.5	0.036
pH	2.3 ± 0.8	2.6 ± 0.6	0.047
Epithelial mucosa	2.3 ± 0.8	2.6 ± 0.5	0.036
Moisture	2.6 ± 0.7	2.9 ± 0.7	0.045
Vaginal Health Index Score	11.6 ± 3.0	13.1 ± 1.9	0.006

Table 3.
Comparison of Female Sexual Function Index between pre-treatment and post-treatment phases.

Female Sexual Function Index parameters	Pre-treatment (Mean ± Standard Deviation)	Post-treatment (Mean ± Standard Deviation)	p
Desire	3.7 ± 1.1	4.0 ± 0.7	0.126
Arousal	3.2 ± 0.7	3.4 ± 0.3	0.082
Lubrication	2.8 ± 0.7	3.1 ± 0.4	0.014
Orgasm	3.3 ± 1.0	3.7 ± 0.7	0.031
Satisfaction	3.8 ± 0.8	4.1 ± 0.4	0.027
Pain	2.8 ± 1.3	3.3 ± 0.7	0.024
Female Sexual Function Index score	19.5 ± 3.9	21.4 ± 2.0	0.005

DISCUSSION

Sexual wellbeing has attracted growing attention and increased in importance over recent decades, both for men and women. Since the first pioneering studies in 1960, researchers have taken many steps forward in understanding the complex mechanisms behind female sexuality^(26,27). In addition to the important psychological aspects that may affect it⁽²⁸⁾, there is mounting evidence to suggest that the vaginal microenvironment plays a pivotal role in modulating moisture and pain perception during intercourse⁽²⁹⁻³¹⁾. Although vaginal cytokine levels are not linked to postmenopausal vulvovaginal symptoms⁽³²⁾, it is possible that hormonal modifications (especially in post-menopause) may alter the vaginal microbiome and leukocyte polarization^(33,34), two key elements responsible for pain modulation⁽³⁵⁾.

Several treatments have already been developed to improve vaginal epithelialization and ameliorate related symptoms and signs⁽³⁶⁻³⁸⁾, although the available studies differ significantly in terms of the methods used and thus in the results obtained, making it difficult to identify the best approach. Very few studies have investigated the effects of Aloe and silver ions on the vaginal microenvironment, although this data could be misinterpreted since in most studies the researchers mixed these two compounds with others⁽³⁹⁾, or data analysis was based on animal models⁽⁴⁰⁾. To the best of our knowledge, this is the first report on the effects of silver ions and extracts of Aloe Vera in patients with vaginal de-epithelialization.

Our analysis demonstrated a significant improvement in both the VHIS ($p=0.006$) and FSFI ($p=0.005$), which can be considered direct (VHIS) and indirect (FSFI) signs of increased vaginal epithelialization. On the one hand, all the most

important vaginal health parameters increased, whereas on the other hand the latter indirectly ameliorated female sexual functions. Indeed, all the FSFI parameters increased significantly, with the exception of desire and arousal, which may be more dependent on the patient's psychological state⁽⁴¹⁾.

Despite our significant results, the study was affected by several limitations. Firstly, we did not use a control group, although we opted for this study design since it would have been unethical not to provide any therapy to patients with vaginal de-epithelialization or to administer them a placebo. Moreover, our study was not blind, so patients and researchers were all aware of the purpose of the investigation and the drugs being used. What is more, our analysis was limited to the post-menopausal period and the study population was quite small.

Considering these latter elements, we would like to take this opportunity to encourage future studies with greater statistical power, which may confirm our results within larger cohorts. Furthermore, future research should explore whether treatment with silver ions and Aloe Vera extract could increase vaginal fluid levels of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which are the most important mediators responsible for re-epithelialization.

DECLARATION OF INTEREST

This study did not receive any grants or funding. The authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company.

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