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Vaginal injections of non-crosslinked hyaluronic acid for the relief of vaginal dryness symptoms. A case series

Dopochwowe iniekcje nieusieciowanego kwasu hialuronowego w niwelowaniu objawów suchości pochwy. Seria przypadków

ABSTRACT

Introduction: Vaginal dryness and trophic disorders are a common, underreported problem that decreases quality of life. Standard treatments, such as lubricants, moisturizing products, or hormone therapies, do not always produce the desired results or may be contraindicated.

Aim: This study aimed to present the results of a pilot clinical observation regarding intravaginal injections of high-molecular-weight non-crosslinked hyaluronic acid in women with severe symptoms of vaginal mucosal and vestibular dryness.

Materials and methods: Five women with severe symptoms of dryness, itching, burning, and pain during intercourse received a single submucosal injection of non-crosslinked hyaluronic acid (1.6% or 2.2%). The results were evaluated after four weeks. The analysis included self-assessment, medical evaluation of trophic condition, peri-procedural sensations on an 11-point numerical intensity scale (0-10), and treatment safety.

Results: A rapid, clinically significant improvement was observed: the mean self-assessment of lubrication increased from 4.2 to 8.8/10, and itching, burning, and pain during intercourse resolved completely after just one week. A gynecological examination revealed normalization of tissue condition in all areas.

Conclusions: The results are consistent with the mechanism of action of non-crosslinked hyaluronic acid and suggest a potential minimally invasive alternative for women who cannot undergo or do not accept hormonal therapy.

Keywords: non-crosslinked hyaluronic acid, vaginal injection, vaginal dryness, vaginal atrophy, dyspareunia, off-label.

STRESZCZENIE

Wstęp: Suchość pochwy i zaburzenia trofiki to częsty, niedoszacowany problem obniżający jakość życia. Standardowe metody leczenia, takie jak lubrykanty, preparaty nawilżające czy terapie hormonalne, nie zawsze przynoszą oczekiwane efekty lub mogą być przeciwwskazane.

Cel: Celem pracy było przedstawienie wyników pilotażowej obserwacji klinicznej dotyczącej dopochwowych iniekcji nieusieciowanego kwasu hialuronowego o wysokiej masie cząsteczkowej u kobiet z nasilonymi objawami suchości błony śluzowej i przedsionka pochwy.

Materiały i metody: U pięciu kobiet z nasilonymi objawami suchości, świądu, pieczenia oraz bólu podczas współżycia wykonano jednorazową, podśluzówkową iniekcję nieusieciowanego kwasu hialuronowego (1,6% lub 2,2%). Ocenę przeprowadzono po 4 tygodniach. Analizowano samoocenę, ocenę lekarską trofiki, doznania okołozabiegowe w 11-stopniowej numerycznej skali natężenia (0-10) oraz bezpieczeństwo terapii.

Wyniki: Odnotowano szybką, klinicznie istotną poprawę: średnia samoocena nawilżenia wzrosła z 4,2 do 8,8/10, a świąd, pieczenie i ból podczas współżycia ustąpiły całkowicie już po tygodniu. W badaniu ginekologicznym stwierdzono normalizację trofiki we wszystkich domenach.

Wnioski: Wyniki są zgodne z działaniem nieusieciowanego kwasu hialuronowego i wskazują na potencjalną małoinwazyjną alternatywę dla kobiet, które nie mogą lub nie akceptują terapii hormonalnej.

Słowa kluczowe: nieusieciowany kwas hialuronowy, iniekcja dopochwowa, suchość pochwy, atrofia pochwy, dyspareunia, *off-label*.

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INTRODUCTION

Vaginal dryness and vaginal atrophy are common, yet still under-recognised clinical problems. In genitourinary syndrome of menopause (GSM; previously termed vulvovaginal atrophy, VVA), vaginal dryness and atrophic changes affect 35-90% of postmenopausal women, but they may also occur in other hypoestrogenic states, including after oncological treatment, during the postpartum period, or while receiving selected anti-estrogen therapies. Symptoms such as dryness, burning, pruritus, and dyspareunia affect not only sexual function but also everyday comfort and quality of life. Standard management includes intravaginal moisturisers and lubricants, although their effects are usually short-lived. Local or systemic hormonal therapies are also used, including estrogen therapy, selective estrogen receptor modulators (SERMs), and dehydroepiandrosterone (DHEA), but these options may be contraindicated or unacceptable for some patients. At the same time, non-pharmacological approaches, such as laser-based therapies, injection-based treatments [1], and urogynecological physiotherapy, are being developed; however, publications assessing their long-term efficacy vary in methodological quality and do not provide fully consistent evidence [2-4].

The underlying cause of these symptoms is primarily estrogen deficiency and the resulting changes in the vaginal mucosa and extracellular matrix (ECM), including dehydration of the ECM, reduced glycosaminoglycan content (including hyaluronic acid), alterations in the collagen I/III ratio, flattening of the mucosal architecture with epithelial thinning, increased vaginal pH, and a reduction in *Lactobacillus* species, all of which lead to impaired tissue elasticity and integrity. These physiological changes result in reduced hydration and elasticity of the vaginal fornix, together with a rise in pH. The labia minora become thinner and hypotrophic, the vaginal rugae disappear, and the introitus recedes and loses its elasticity, often leading to severe pain on penetration (introital dyspareunia), burning, irritation, and postcoital spotting [3-5].

Hyaluronic acid (HA) is a key component of the extracellular matrix, including the vaginal mucosa. This polysaccharide, belonging to the glycosaminoglycan family, is responsible for water binding, the viscoelastic properties of tissues, and a microenvironment that supports cell migration and proliferation; it also participates in tissue healing and remodelling [6]. HA is widely used in aesthetic medicine [7], and in recent years its applications in aesthetic gynaecology have been intensively investigated, for example, in labial rejuvenation and augmentation [8-10], as well as in selected gynaecological disorders, particularly those associated with impaired vaginal hydration [11, 12]. Several randomised controlled trials have shown that HA alleviates symptoms of vaginal atrophy; however, these studies have focused on topical formulations such as gels or vaginal ovules [13-16]. Given the endogenous nature of HA, direct administration into the superficial layers of the mucosa (submucosally) appears particularly justified, as this is where its regenerative and hydrating potential may be most fully expressed. Both molecular weight and the degree of crosslinking are important. High-molecular-weight, non-crosslinked HA exerts primarily hydrating and regenerative effects, whereas crosslinked HA may be used to achieve a volumising effect [7, 11].

In recent years, reports have emerged suggesting that HA injections into the vaginal vestibule and vagina may reduce dryness-related symptoms, burning, and dyspareunia, while also improving sexual function. Among other findings, favourable tissue-related changes at the molecular level have been demonstrated, including increased expression of the COL1A1 and COL3A1 genes [17], as well as improvements in pain scores measured with the Visual Analogue Scale (VAS) and in the Female Sexual Function Index (FSFI) in patients with provoked vestibulodynia (PVD) [18] and symptoms of vulvovaginal atrophy. Both non-crosslinked/stabilised HA protocols [19, 20] and studies using crosslinked preparations [16] have been published, including comparative studies with control groups [21, 22]. Equally important as efficacy is the safety of products administered intradermally or submucosally. A favourable safety profile generally characterises injectable HA medical devices; however, the literature describes rare but severe events associated with insufficient operator qualification or improper injection technique in the genital area, including pulmonary embolism and diffuse alveolar haemorrhage, underscoring the need for rigorous aseptic precautions, strict adherence to injection technique, and appropriate operator training [23].

AIM

This study aimed to present the results of a pilot outpatient clinical observation (a case series from routine clinical practice) evaluating the effectiveness and tolerability of a single submucosal injection of non-crosslinked HA used off-label in women with pronounced symptoms of vaginal dryness and vaginal atrophy. Effectiveness was assessed in parallel on the basis of patient self-assessment and objective clinician evaluation, while treatment safety was evaluated through peri-procedural sensations and active monitoring of adverse events.

MATERIALS AND METHODS

This outpatient clinical observation, designed as a case series, was conducted in a gynaecology practice in Gdańsk (Poland) over a period of two months. It aimed to provide both qualitative and quantitative assessment of the effectiveness and safety of a single intravaginal injection of non-crosslinked HA used off-label (i.e. in a manner differing from the manufacturer's instructions for use with regard to intravaginal administration) for the alleviation of vaginal mucosal and vestibular dryness. The analysis included five women aged over 35 years with

pronounced symptoms of dryness of the vaginal mucosa and vaginal vestibule (at least 7/10 on a physician-assessed severity scale). Women were not eligible for inclusion if they were pregnant or breastfeeding, menstruating on the day of qualification, experiencing genital tract bleeding, or had an active vulvar/vaginal infection or other pathology of the genital organs. Additional exclusion criteria included coagulation disorders, a history of cancer, and other conditions, therapies, or procedures that could interfere with the interpretation of the observation results. This report is presented as a case series derived from routine outpatient clinical practice. Before the procedure, each participant received detailed information about the course, including the off-label nature of the intervention, the potential benefits, possible risks and limitations, and available alternatives. An eligibility assessment was performed to exclude contraindications, after which written informed consent was obtained. It was emphasised that, although injections of non-crosslinked HA are minimally invasive, they may be associated with adverse effects. The patients also provided written consent for the use of anonymised clinical data for scientific and publication purposes.

During the clinical observation, two injectable gels based on high-molecular-weight, non-crosslinked sodium hyaluronate were used: Flavya Medium (1.6% sodium hyaluronate) and Flavya Excellence (2.2% sodium hyaluronate), both classified as class III medical devices. The sodium hyaluronate used in these products was of non-animal origin and manufactured by microbial fermentation. Both preparations were supplied in sterile, single-use prefilled 2 mL syringes, packaged in blister packs. The products were used off-label based on the treating physician's clinical judgement, following an individual benefit–risk assessment and the patients' written informed consent for the use of the product outside its approved indication.

After the qualification visit (V0), which included a medical history interview, a gynaecological examination, and baseline scale-based assessments, the procedure was performed on the same day (V1). In all participants, topical anaesthesia with lidocaine gel and local anaesthesia with injectable lidocaine hydrochloride were used. During this visit, non-crosslinked HA was administered as a single intravaginal injection using a multipoint technique, submucosally into the vaginal vestibule as well as the posterior and lateral vaginal walls. Before the procedure, the participants completed an author-designed questionnaire consisting of two parts. The qualitative section used a four-point scale ("very unsatisfactory", "rather unsatisfactory", "rather satisfactory", "very satisfactory") and assessed the impact of vaginal mucosal dryness on quality of life, including overall hydration, sense of attractiveness and self-confidence, comfort during physical activity, comfort when wearing underwear, pleasure during intercourse, and desire for intercourse. The quantitative section assessed the severity of dryness, pruritus, burning, and pain during intercourse on a 0-10 scale. Immediately after product administration, procedure-related sensations were recorded using the numerical rating scale (NRS). This scale was based on the participants' subjective assessment of symptom intensity and ranged from 0 to 10, where 0 indicated complete absence of pain, stinging, burning, or pressure, and 10 indicated the worst imaginable pain, stinging, burning, or pressure. The physician documented the clinical assessment in the observation form, including hydration of the vaginal mucosa and vestibule on a 0-10 scale, as well as elasticity/wall tone, mucosal thickness and colour, and epithelial integrity on a 1-3 scale. Follow-up was conducted by telephone at weeks 1, 2, and 3 after V1 to assess symptoms, satisfaction, safety, and any changes in pharmacotherapy, while the follow-up visit (V2) took place after 28 ± 2 days and included a clinical assessment by the physician and self-assessment. Subsequently, two further telephone questionnaires were completed at 2 and 4 weeks after V2. Throughout the observation period, the physician continuously monitored procedural safety, recording and classifying any adverse events in accordance with the observation form. At the final visit, each participant completed a satisfaction questionnaire focused on overall satisfaction with the procedure and the perceived effectiveness in improving hydration of the vaginal mucosa and vestibule.

The clinical observation was conducted in a group of five women with pronounced symptoms of vaginal dryness. Complete clinician assessments were obtained for all participants at visits V1 and V2, although telephone follow-up data were incomplete for participant P5. Owing to the small number of participants, the results were presented in the form of case descriptions.

RESULTS

In the analysis of five participants, mean self-rated vaginal mucosal hydration (0-10 scale) increased from 4.2 at baseline to 8.8 four weeks after the procedure, while the median increased from 5 to 9. Improvement was observed in every participant. The pattern of change indicated a rapid increase in effect during the first two to three weeks after injection, followed by maintenance of the achieved values until the end of the observation period. The highest scores were recorded between the first and third week after the procedure (Fig. 1).

A similar pattern of change was also observed in the clinician assessment. Vaginal mucosal hydration scores (0-10 scale) increased in all assessed women between the baseline and control visits, reaching 7-10 points at V2 (Fig. 2).

The clinical assessment performed by the physician during gynaecological examination also demonstrated normalisation of the mucosa and tissue appearance in all analysed participants. At baseline, scores of 2-3 predominated on the three-point scales for vaginal wall tone, mucosal thickness

and colour, and epithelial integrity, whereas at the 4-week follow-up visit, each of the five participants scored 1 in all domains, corresponding to a normal clinical appearance (Fig. 3).

Subjective symptoms resolved rapidly and completely. In all cases in which baseline severity exceeded 5 points — participant P3: pruritus (7 points), burning (7 points), and pain during intercourse (6 points) — the scores decreased to 0 within one week after the procedure and remained at this level until the end of the 8-week observation period. Similarly, in cases of moderate severity, with baseline scores of 5 points (pruritus in participant P1 and pain during intercourse in participant P2), the scores decreased to 0 after 1 week and remained unchanged in subsequent assessments. No recurrence of pruritus, burning, or dyspareunia was observed at any of the monitored time points.

Satisfaction ratings were consistent with the observed clinical improvement. Across the six domains assessing the impact of improved hydration on daily functioning — overall hydration, sense of attractiveness and self-confidence, comfort during physical activity, comfort when wearing underwear, pleasure during intercourse, and desire for intercourse — responses of "very satisfactory" predominated at V2. Only isolated domains were rated as "rather satisfactory". In comments collected during the weekly telephone follow-up, the participants repeatedly emphasised that the most noticeable and clinically meaningful improvement was the reduction in pain and discomfort during intercourse. They noted that vaginal and mucosal dryness may be less apparent in everyday life, whereas it becomes most pronounced during sexual activity; therefore, the rapid reduction of this symptom domain to 0 was regarded as particularly important and most satisfying. In the final questionnaire with dichotomous (yes/no) items, all participants who completed it confirmed satisfaction with the outcomes, declared willingness to continue therapy, and

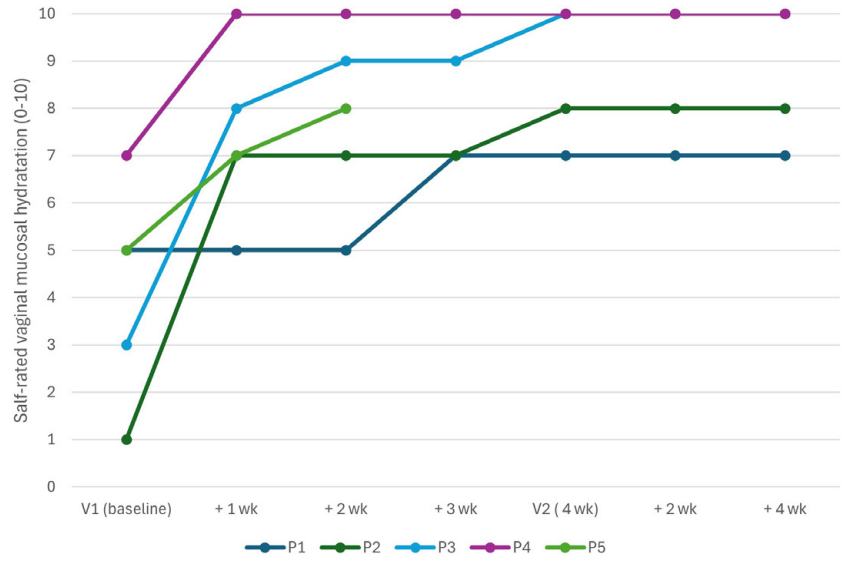

Fig. 1. Change in self-rated vaginal mucosal hydration (0–10 scale): before the procedure (V1), at weeks 1, 2, and 3 after V1, at the control visit (V2), and at 2 and 4 weeks after V2. The analysis includes five participants (P1–P5). **Source:** Authors' own elaboration.

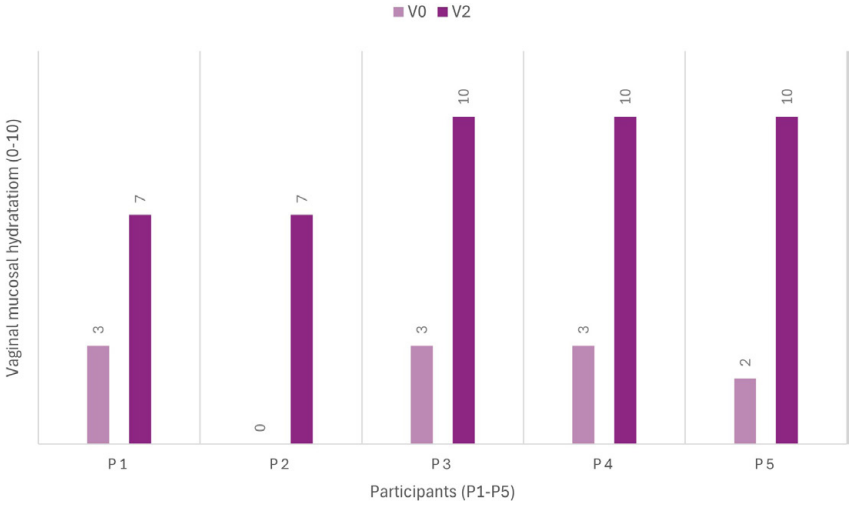

Fig. 2. Clinician-assessed vaginal mucosal hydration at the qualification visit (V0) and at the control visit (V2) (4 weeks after the procedure) in five participants (P1–P5). **Source:** Authors' own elaboration.

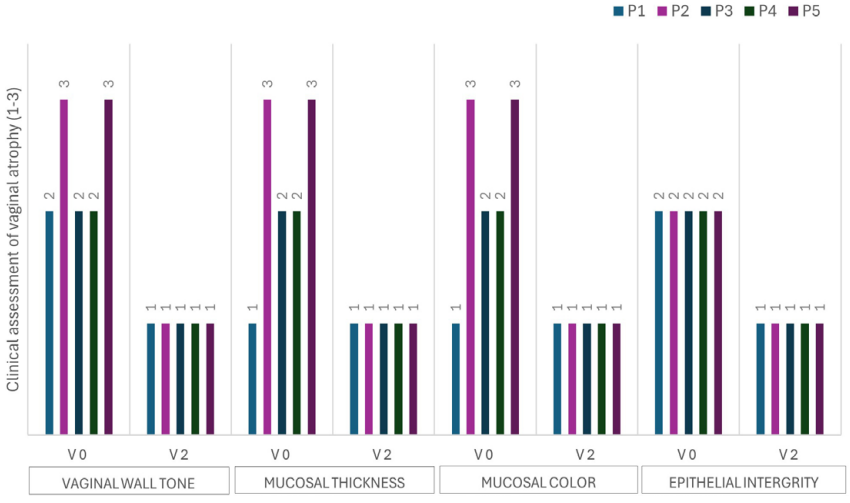

Fig. 3. Clinical assessment of vaginal atrophy performed across four domains — vaginal wall tone, mucosal thickness and colour, and epithelial integrity — using a 1–3 scale (1 = normal finding, 3 = unfavourable finding), at the qualification visit (V0) and at the control visit (V2) in five participants (P1–P5). **Source:** Authors' own elaboration.

indicated that they would recommend the procedure to other women.

Immediately after the procedure, the participants rated injection-related sensations using an 11-point NRS (0-10). The scores remained low: pain – median 1 (mean 1.0), stinging 1 (1.2), burning 0 (0.6), and pressure 1 (1.6). The highest single score concerned pressure (5/10) in one participant; all other measurements did not exceed 3/10, indicating low pain intensity. No complications or side effects were observed during or after the procedures, confirming good tolerability of the intervention in this case series. The safety of intravaginal injections was actively monitored throughout the entire observation period (visits and telephone follow-up), with any potential adverse events recorded and classified in the observation documentation. No adverse events were reported.

DISCUSSION

In this case series, a single injection of high-molecular-weight, non-crosslinked HA was associated with a rapid and clinically meaningful improvement in both patient self-assessment and the objective clinical evaluation of vaginal atrophy. It should be emphasised, however, that in the present case series, the medical device was used outside the manufacturer's intended indication. This report is observational in nature and should not be regarded as a clinical recommendation or as encouragement for routine use of the product in a manner inconsistent with its intended purpose. It is also important to note that symptoms of genitourinary syndrome may occur before menopause when associated with hypoestrogenism (e.g. in the postpartum period, after oncological treatment, or during the use of selected anti-estrogen or contraceptive therapies) [1, 19]. According to other publications, this condition affects more than 20% of premenopausal women [2], which justifies the inclusion of both postmenopausal and premenopausal women in this observation, better reflecting the real-life spectrum of women presenting with vaginal dryness related to atrophic changes and dyspareunia in routine outpatient practice.

According to collected results, hydration improved progressively over the following weeks, reaching its peak in the second to third week, and was maintained throughout the 8-week follow-up period. Symptoms such as pruritus, burning, and pain during intercourse declined to 0 on the 0-10 scale within one week at the latest and did not recur at subsequent time points. The participants repeatedly emphasised that the resolution of dyspareunia was the most important indicator of treatment effectiveness for them, as this is the domain in which dryness and atrophic vaginal changes are experienced most acutely. This effect is of clear clinical relevance, since many postmenopausal women remain sexually active. In a large population-based study involving approximately 94,000 women aged 50-79 years, more than half (around 52%) reported having had sexual intercourse within the previous year [24]. In this context, the rapid resolution of pain and discomfort during intercourse following injection of non-crosslinked HA translated directly into improved quality of life in the present case series. The conclusions drawn from this clinical observation are consistent with reports from other authors who, using validated assessment tools (VAS and FSFI), also demonstrated significant improvement in symptoms of atrophy and sexual dysfunction after injections of non-crosslinked HA, with the median FSFI increasing from 20.8 to 28.3 points after one month [19].

Non-crosslinked HA was deliberately selected because it most closely resembles the physiological hyaluronan naturally present in the vaginal mucosa. It strongly binds water, improves tissue hydration and viscoelasticity, and contributes to a microenvironment that supports cell migration, proliferation, and reparative processes, including through interactions with the CD44 receptor and modulation of extracellular matrix remodelling [6]. Clinically, this translates into improved hydration and tissue repair without the prolonged volumising effect characteristic of crosslinked preparations [10, 11]. At the time this observation was conducted, the availability of products intended for injectable use in the vagina was limited in routine clinical practice, and the authors did not have access to a product with a comparable profile (high-molecular-weight, non-crosslinked HA) that was specifically indicated for such use. Available crosslinked HA products are designed primarily to provide a volumising effect and prolonged gel persistence, which, in the authors' clinical judgement, did not correspond to the needs of the patients in this case series, whose treatment goals were improvement of hydration and reversal of atrophic changes. It should be noted, however, that the literature also describes HA-based products enriched with additional biostimulants, such as calcium hydroxyapatite, which promotes collagen synthesis and may enhance regenerative effects [20]. Differences in the rheological and pharmacokinetic properties of HA preparations are also important: crosslinking increases viscosity and prolongs gel persistence for volumising purposes, whereas non-crosslinked preparations diffuse more readily within the submucosal layers, enabling targeted hydrating effects [7]. From the perspective of tissue biology, the effects observed in this study – rapid resolution of pain during intercourse and gradual improvement in hydration – are consistent with these properties: rehydration reduces friction and the risk of microtrauma, while the presence of HA in the submucosal layer influences the extracellular matrix and supports reparative processes [11]. Although no histological assessments were performed, the consistency between patient self-assessment and clinician evaluation suggests that the observed benefit extended beyond a simple "lubricating" effect and included improvement in mucosal quality and epithelial integrity. These findings add to the still limited body of evidence regarding injectable non-crosslinked HA for vaginal atrophy and related symptoms [18, 19] (most reports concern topical

formulations [12-15] or crosslinked products [16, 20, 21]) and support the hypothesis that submucosal injection of non-crosslinked HA may represent a valuable minimally invasive option, particularly for women with contraindications to hormonal therapy or those who do not accept such treatment.

Although intravaginal administration of HA is an injection-based procedure, when performed under aseptic conditions, using proper technique and by appropriately qualified personnel, it may be regarded as minimally invasive. In the present case series, no complications were observed either during or after the procedure, confirming a favourable tolerability profile. This intervention avoids some of the typical limitations of topical treatment and pharmacotherapy, such as the need for daily application, the necessity of planning sexual intercourse, or variability in dosing, while offering an effect achieved through a single, short procedure. At the same time, the cases described here may support the need to explore alternative therapeutic options for women with contraindications to estrogen therapy (e.g. after breast cancer) or for those who do not accept hormonal treatment, in whom non-hormonal interventions should be considered first-line. In this series, product tolerability was also supported by low NRS scores for procedure-related sensations after standard local anaesthesia. Moreover, clinical studies of non-crosslinked HA combined with a biostimulant have demonstrated significant histologically confirmed improvement in vaginal atrophy, together with subjective and objective improvement in urinary incontinence, suggesting that this therapeutic approach may have broader clinical applications [20].

A limitation of this case series is the inability to obtain tissue for histopathological examination, as well as the small sample size, which precludes statistical inference. The monitoring period lasted 8 weeks, which was sufficient to assess early and intermediate effects and tolerability, but not to evaluate the durability of the results. It should be noted, however, that longer clinical follow-up periods (up to 12 months) have suggested persistence of positive effects, both in terms of subjective symptoms and improvement in quality of life [19]. A comparative study with randomisation and a control group in a larger population, with extended follow-up (e.g. up to 6 months), would therefore be justified, ideally incorporating objective markers of the vaginal environment, standardised functional instruments (e.g. FSFI, VHI), and imaging methods. In addition, the sample size was too small to allow any conclusions regarding differences between the 1.6% and 2.2% concentrations or the potential need for repeated treatment sessions.

CONCLUSIONS

The present case series suggests that off-label intravaginal injections of non-crosslinked HA may represent a promising, safe, and well-tolerated approach for the management of symptoms of vaginal dryness and vulvar atrophy. A single treatment session resulted in rapid and clinically meaningful improvement in both participant self-assessment and objective clinician evaluation, leading to complete remission of symptoms such as dyspareunia, pruritus, and burning during the observation period. Given that a substantial proportion of postmenopausal women remain sexually active and that hypoestrogenic states may also occur before menopause, this intervention may constitute a potential addition to the available therapeutic options in selected patients, provided that an individual benefit–risk assessment is performed and that full information and informed consent are ensured in the setting of off-label use. Owing to the pilot nature of this observation, further studies – particularly controlled studies involving larger populations – are needed to better assess the effectiveness, durability of effects, and safety profile of this approach, and to provide data that may support any future consideration of extending the manufacturer's approved indication.

ETHICAL CONSIDERATIONS

The medical device was used off-label (i.e. outside the manufacturer's instructions for use with regard to intravaginal administration) as part of routine outpatient practice, following an individual benefit-risk assessment. Before the procedure, written informed consent was obtained from all patients, including consent for off-label use and for the use of anonymised data for scientific and publication purposes. Safety was actively monitored during visits and telephone follow-up. No adverse events or complications were observed in this case series.

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