

The effect of hyaluronic acid (Cicatridine) on healing and regeneration of the uterine cervix and vagina and vulvar dystrophy therapy

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Summary

Procedures aimed at the treatment of precancerous lesions and ectopia on the uterine cervix are frequently linked to lesions of anatomical structures. The application of hyaluronic acid (Cicatridine vaginal ovules) promotes accelerated healing of the uterine cervix and acquisition of a normal shape in the uterine cervix canal. Local application of hyaluronic acid in the vagina following radiotherapy due to cancer in the uterine cervix or endometrium favourably affects the healing of post-irradiation lesions in the vagina and improves quality of life. Over 90% of patients responded positively to the application of hyaluronic acid in the form of a cream on dystrophic lesions in the vulva. Hyaluronic acid aids the healing process of post-procedural wounds in the uterine cervix, following radiotherapy applied due to cancer of the uterine cervix, endometrium and in vulvar dystrophy.

Key words: Hyaluronic acid; Uterine cervix; Dysplasia of uterine cervix; Radiotherapy; Endometrial carcinoma; Cancer of uterine cervix; Dystrophy.

Introduction

Uterine cervix treatment of precancerous lesions or ectopia are linked to surgical, thermal or electric trauma. A significant proportion of females after radiotherapy due to cervical or endometrial cancer suffer post-irradiation reactions in the vagina, involving the thinning and an increasing fragility of the vaginal walls, vasodilation and atrophy. This may lead to a narrowing of the vaginal walls, its adhesion, ulcerations and even to the formation of vesico-vaginal and recto-vaginal fistulas [1, 2]. At the same time, irradiation linked to surgical castration induced by the procedure reduces several functions, thus affecting the quality of life [3-5].

Reparative and remodelling processes within the uterine cervix manifest a variable duration, depending on the type of therapeutic intervention.

During menopause, mainly due to oestrogen deficiency, a significant proportion of women also manifest vulvar lesions. The amount of adipose tissue becomes reduced, collagen fibres disappear, the epithelium becomes thinner and its sublayer demonstrates traits of chronic inflammation, lichen sclerosus. At the time morphotrophic elements of the vulva undergo atrophy: the small pudendal lip and clitoris develop dystrophic lesions. Occasionally, the epithelium is white, thickened and cracked, which is characteristic of a hypertrophic dystrophy [6].

Hyaluronic acid, the main component of Cicatridine, acts on two levels – water retention in the tissues and through binding to proteins and the formation of a proteoglycan network. Thus it improves tissue hydration and the

import of nutrients to the tissue. This results in a normal tissue turgor, its improved elasticity and in epithelial regeneration in atrophy and dystrophy of vaginal mucosa. Through its presence in the extra-cellular matrix and due to its modulating potential as well as due to its promotion of capillary sprouting, hyaluronic acid favourably affects healing processes, including the formation of a normal epithelium [7-9].

The study was aimed at evaluating Cicatridine, applied in the form of ovules (1 ovule contains: 0.005 g sodium salt of hyaluronic acid, 0.06 g – Centella asiatica oil extract (Hydrocotyle asiatica L., Hydrocotyle repanda Pers., Gotu kola), 0.06 g – calendula oil extract, 0.06 g – aloe oil extract, 0.002 g – tea-tree essential oil) in the course of healing and reparation processes following surgical procedures on the uterine cervix, and following radiotherapy applied due to cervical and endometrial cancer as well as at the evaluation of hyaluronic acid applied in the form of a cream (1 g of which contains 0.002 g sodium salt of hyaluronic acid) used in vulvar dystrophy therapy.

Patients and Methods

The total number of 213 women, including 109 patients following procedures involving the uterine cervix due either to CIN I - CIN III (following electrocoagulation) or ectopy of the uterine cervix (following electrocoagulation and cryotherapy), 53 women following radiotherapy due to cancer of the uterine cervix or cancer of the endometrium and 51 women in whom earlier vulvar dystrophy was histologically confirmed.

A control group consisted of 86 patients following procedures on the uterine cervix, following radiotherapy or showing vulvar dystrophy, in whom the studied preparation was not applied. The analysed material is listed in Table 1.

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Table 1. — Patients and the control group.

Groups of patients	Examined group	%	Control group	%
<i>Patients following uterine cervix procedures</i>	109	51.17	42	48.84
with CIN I – CIN III, subjected to electroconization	32		9	
with ectopy of the uterine cervix, subjected to electroconization	43		15	
with ectopy of the uterine cervix, subjected to cryotherapy	34		18	
<i>Patients following radiotherapy</i>	53	24.88	24	27.91
following radiotherapy due to cancer of the uterine cervix	16		12	
following radiotherapy due to cancer of the endometrium	37		12	
<i>Patients with vulvar dystrophy</i>	51	23.94	20	23.26
Total	213	100.00	86	100.00

Table 2. — Women treated with the studied preparation vs control group following procedures on the uterine cervix.

	Examined group					Control group				
	After Weeks		After 3 months			After 6 weeks		After 3 months		
	N	N	%	N	%	N	N	%	N	%
Patients with CIN I - CIN III subjected to electroconization	32	27	84.38 *	32	100.00	9	5	55.56 *	8	88.89
Patients with ectopy of the uterine cervix subjected to electrocoagulation	43	38	88.37	40	93.02	15	11	73.33	12	80.00
Patients with ectopy of the uterine cervix subjected to cryotherapy	34	34	100.00 *	34	100.00	18	12	66.67 *	18	100.00
Total	109	99	90.83 *	106	97.25	42	28	66.67 *	38	90.48

* $p < 0.05$

In patients following procedures on the uterine cervix aimed at accelerated re-epithelization, the application of hyaluronic acid in the form of vaginal ovules was started 24 hours after the operation.

In patients following radiotherapy, indications for the treatment involved the detection of inflammatory/necrotic lesions in the vagina, adhesions of vaginal walls and complaints associated with coitus after the completion of brachytherapy. Vaginal ovules of the preparation were applied once daily, in the evening for ten subsequent days and, then, for a period of one month, every second day and, in cases showing improvement, for a further month every third day.

In women with vulvar dystrophy cream containing hyaluronic acid was applied for a month; it was applied to affected sites twice a day. In cases of improvement the procedure was recommended to be continued for a further three months and, then, for two months, applying it at night. Patients in the control group applied no therapy following procedures on the uterine cervix and radiotherapy. Women in the control group and those affected by vulvar dystrophy included patients who following diagnosis did not want to participate in the therapy and decided to follow hygienic procedures only.

Results of the treatment were evaluated after six weeks and three months, and women treated with vaginal ovules of the preparation were evaluated by visual examination of the uterine cervix and/or vagina and patient feeling. In women with vulvar dystrophy treated with hyaluronic acid, evaluation was conducted one, three and six months after termination of the therapy by visual inspection and comfort of the patients.

Statistical evaluation was performed by statistical software, using the Wilcoxon and the Mann-Whitney U tests.

Results

Most of the examined women (99-90.83%) in whom Cicatridine vaginal ovules were applied following operations on the uterine cervix due to CIN I-CIN III and

ectopy of uterine cervix after six weeks demonstrated a healed cervix with no deformations or endometriotic foci and in none of the cases did the cervical canal outlet demonstrate any narrowing.

In the control group only 28 women (66.67%) achieved a similar result. Following three months, 106 women of the treated group (97.25%) had a healed cervix while in the control group the fraction of patients was only slightly lower (90.48%) (Table 2).

In patients following radiotherapy treated with vaginal ovules of the preparation a healed vagina was noted in 12 women (22.64%) and improvement was detected in 45 women (84.91%). In the control group no healing or improvement could be detected in any of the patients during the three-month observation period (Table 3).

In the group of 51 women with vulvar dystrophy a positive response to treatment with cream containing the examined substance was noted in 46 patients (90.2%) and in a significant fraction (64.71%) the group consisted of healthy, asymptomatic patients. In patients not exposed to cream, hygienic management resulted in a response in 65% women but in such cases just improvement, not total elimination of the symptoms could be noted (Table 4).

Discussion

Procedures on the uterine cervix, performed due to pre-cancerous lesions (CIN) or ectopy, are linked to a more or less extensive tissue lesion, associated with various complaints, including bleeding, spotting, excessive discharge, fibrosis, endometriosis, narrowing of the uterine cervical canal and a psychological discomfort reflecting the fear that sexual contact may negatively affect the healing process.

Table 3. — Women administered the examined preparation vs the control group following radiotherapy due to cancer of the uterine cervix and/or cancer of the endometrium.

	Examined group					Control group				
	Healing after 3 months		Improvement after 3 months		Healing after 3 months		Improvement after 3 months			
	N	%	N	%	N	%	N	%		
Patients following radiotherapy due to cancer of the uterine cervix	16	4	25.00	13	81.25*	12	0	0.00	0	0.00*
Patients following radiotherapy due to endometrial cancer	37	8	21.62	32	86.49*	12	0	0.00	0	0.00*
Total	53	12	22.64	45	84.91*	24	0	0.00	0	0.00*

Table 4. — Results of observation in patients affected by vulvar dystrophy (preparation vs placebo).

	Examined group		Control group	
	N	%	N	%
Healthy asymptomatic women	33	64.71*	0	0.00*
Improvement	13	25.49*	13	65.00*
Stabilization	1	1.96	0	0.00
Deterioration	4	7.84	7	35.00
Total	51	100.00	20	100.00
Positive response	46	90.20*	13	65.00*

* $p < 0.05$

The results of our earlier studies, on a lower number of patients, indicated that locally applied Cicatridine preparation accelerated repair processes to a variable extent, depending on the type of procedure on the uterine cervix [10]. In a higher number of women following procedures on the uterine cervix we have confirmed that hyaluronic acid accelerates the healing processes and prevents narrowing of the canal in the uterine cervix. It is quite possible that this involves the same mechanism which prevents development of adhesions after application of hyaluronic acid following abdominal operations in an animal model [11].

Radiotherapy, used following oncological surgery in the treatment of uterine cervix cancer or cancer of the endometrium, induces port-irradiation injury overlapping with castration-linked hypoestrogenism. This represents a significant problem of deteriorated life quality while the decreasing pH in the vagina is linked to reduced sexual satisfaction [1-4, 12].

Studies of Katz [1] and those of Lorenz *et al.* [2] demonstrated that irradiation induced dryness and narrowing of the vagina and in 26% of females it resulted in late post-irradiation reactions, which had a strong negative impact on sexual function, and in this way decreasing the quality of life.

Application of vaginal ovules with the studied preparation has induced healing of the vaginal lesions in over 20% of the patients (Table 3) and an improved vaginal outlook and subjective perception in over 80% of the patients. Such activity has been confirmed by other authors both in animal models and in the course of second-look operations, which have demonstrated the anti-adhesion effects of hyaluronic acid [11, 13].

In the therapy of vaginal dystrophy we see a continuous

introduction of novel therapeutic methods. Ayhan *et al.* [6] obtained a satisfactory clinical response to the application of testosterone and corticoids in such patients but they were not accompanied by histological improvement. In the last ten years the photodynamic method of treating vulvar pathology has been introduced, which proved to be effective following a variable period of application (on average after 6 months) but the disease relapsed [14, 15].

In conclusion, intense application of Cicatridine is non-invasive, easy to implement and inexpensive, and in our group of 51 patients it resulted in a favourable effect of the treatment in over 90% of the patients.

References

- [1] Katz A.: "Interventions for sexuality after pelvic radiation therapy and gynecological cancer". *Cancer J.*, 2009, 15, 45.
- [2] Lorenz E., Strickert T., Hagen B.: "Cervical carcinoma: postoperative radiotherapy: fifteen year experience in a Norwegian health region". *Int. J. Gynecol. Cancer*, 2009, 19, 1595.
- [3] Guaschino S., Benvenuti C.: "SOPHY Study Group SOPHY project: an observational study of vaginal pH and lifestyle in women of different ages and different physiopathological conditions. Part. I". *Minerva Ginecol.*, 2008, 60, 105.
- [4] Jensen P., Groenvold M., Klee M., Thranov I., Petersen M.A., Machin D.: "Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer". *Int. J. Radiat. Oncol. Biol. Phys.*, 2003, 56, 937.
- [5] Nashiro T., Yagi C., Hirakara M., Inamine M., Nagai Y., Sakumoto K. *et al.*: "Concurrent chemoradiation for locally advanced squamous cell carcinoma of the vagina: case series and literature review". *Int. J. Clin. Oncol.*, 2008, 13, 335.
- [6] Ayhan A., Tuncer Zs., Kaya H.: "Vulvar dystrophy: an evolution of 285 cases". *Eur. J. Gynaecol. Oncol.*, 1997, 18, 139.
- [7] Jackson S., James M., Abrams P.: "The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence". *BJOG*, 2002, 109, 339.
- [8] Gerdin B., Hallgren R.: "Dynamic role of hyaluronan (HA4) in connective tissue activation and inflammation". *J. Intern. Med.*, 1997, 242, 49.
- [9] Kaya G., Tran C., Sorg O., Hotz R., Grand D., Carraux P. *et al.*: "Hyaluronate fragments reverse skin atrophy by a CD44 - dependent mechanism". *PLoS Med.*, 2006, 3, 493.
- [10] Markowska J., Markowska A., M dry R.: "Evaluation of Cicatridine efficacy in healing and repairing process of uterine cervix, vagina and vulva-open no-randomized clinical study". *Gin. Pol.*, 2008, 79, 494.
- [11] Falabella C.A., Chen W.: "Cross-linked hyaluronic acid films to reduce intra-abdominal postsurgical adhesions in an experimental model". *Dig. Surg.*, 2010, 26, 476.
- [12] Greimel E.R., Winter R., Kapp K.S., Haas J.: "Quality of life and sexual functioning after cervical cancer treatment: a long-term follow-up study". *Psychooncology*, 2009, 18, 476.

- [13] Lundroff P., van Geldorp H., Tronstad S.E., Lalos O., Larsson B., Johns D.B., di Zerega G.S. *et al.*: "Reduction of post-surgical adhesions with ferric hyaluronate gel: a European study". *Hum. Reprod.*, 2001, 16, 1982.
- [14] Hillemanns P., Untch M., Pröve F., Baumgartner R., Hillemanns M., Korell M. *et al.*: "Photodynamic therapy of vulvar lichen sclerosis with 5-aminolevulinic acid". *Obstet. Gynecol.*, 1999, 93, 71.
- [15] Hillemanns P., Wang X., Staehle S., Michels W., Dannecker C. *et al.*: "Evaluation of different treatment modalities for vulvar intraepithelial neoplasia (VIN): CO₂ laser vaporization, photodynamic therapy, excision and vulvectomy". *Gynecol. Oncol.*, 2006, 100, 271.

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