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Efficacy of treatment of HPV-related CIN1 with a vaginal spray composed of Carboxymethyl glucan-Curcumin-Resveratrol-Epicatechin gallate (CCREg): a preliminary study

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ABSTRACT

Objective. HPV-related Cervical Intraepithelial Neoplasia (CIN) lesions require several years to evolve into invasive forms and can often regress spontaneously; according to the current national guidelines, patients aged between 25-64 undergo screening examinations with either a PAP Test (under 30 years of age, every 3 years) or HPV-DNA Test (above 30 years of age, every 5 years); if HPV test is positive, a confirmatory PAP Test is required. In the case of CIN1 lesions, patients undergo check-ups every 12 months to monitor possible changes; if the lesion does not regress within 24 months from the diagnosis, cervical conization is performed. A mixture of Carboxymethyl glucan, Curcumin, Resveratrol, and Epicatechin gallate (CCREg) in the form of a vaginal spray can support reepithelization and provide antioxidant, anti-inflammatory, and antitumoral effects.

Materials and Methods. 90 patients diagnosed with CIN1 lesions between the age of 25 and 55 were included in the study and divided into two groups: 45 patients underwent treatment with CCREg vaginal spray and 45 did not undergo any therapy for a 6-month period. Within each group, three age subgroups were identified (25-35 years old; 36-45 years old; 46-55 years old) in order to stratify the results.

Results. The patients that used the CCREg vaginal spray had a higher spontaneous regression rate compared to the control group in all age subgroups, in particular among patients aged between 25-35.

Conclusions. Thanks to its antioxidant, anti-inflammatory, and antitumoral effects, CCREg vaginal spray can favour a higher probability of regression of CIN1 lesions.

INTRODUCTION

Cervical Intraepithelial Neoplasia (CIN) is the result of a viral infection caused by the Human Papilloma

Virus (HPV), a very common DNA virus that can infect the cells lining several organs of the female genital apparatus (uterine cervix, vagina, vulva) and those of the perianal and oropharyngeal regions.

There are over 200 strains of HPV but most of cervical cancers are caused by high-risk human papilloma virus (HR-HPV) (HPV 16-18).

HPV is transmitted primarily through sexual intercourse. Although two-thirds of sexually active women will come in contact with HPV throughout their lives, a long time is required for the transformation of preneoplastic lesions, namely CIN (Cervical Intraepithelial Neoplasia), VAIN (Vaginal Intraepithelial Neoplasia), VIN (Vulvar Intraepithelial Neoplasia) and AIN (Anal Intraepithelial Neoplasia), into cancerous ones [1-3]. Moreover, a relevant proportion of cases will be eradicated by the immune system without the women being aware of having contracted the infection [4]. In a reduced percentage of cases, however, the virus will be able to multiply and incorporate its DNA within the DNA of host's cells, leading over the years to the formation of atypical cells and, ultimately, to precancerous lesions [5].

Not all lesions progress, and most low-grade lesions (CIN1) tend to regress spontaneously in up to 57-60% of cases (**Table 1**) [6], with a higher regression rate in women below 30 years of age [7]; women diagnosed with CIN1 should be managed by follow-up and require to be treated only in rare cases [8]. The greatest risk in the management of an LSIL, given the limited sensitivity of the PAP Test, is to misdiagnose a high-grade lesion; this can occur because of diagnostic difficulties related to histologic reading, unsatisfactory or topographically unsuitable biopsies related to the diagnosis of squamocolumnar junction (SCJ), the extent of the lesion, multifocality, and the colposcopist's experience [9-12].

The progression time from intraepithelial lesions (CIN) to invasive forms can be extremely long (from 10 to 20 years), although it is possible in short periods of time (<12 months) for initial lesions to transform into invasive forms. The progression of CIN into cervical carcinoma depends on the grade of the lesion, the age of the patients, host-related cofactors (including HPV genotype, viral load, cervicovaginal microbiota, immune state), and

exogenous or environmental cofactors (number of partners, number of pregnancies, smoke, oral contraceptives, coinfections, antioxidizing nutrients) [13].

This disease is susceptible to highly effective treatment. The risk of recurrence following surgery for high grade lesions cannot be underestimated and it is strictly linked to persistence of HPV virus at twelve months and to involvement of endocervical margins [14].

The mixture of Carboxymethyl glucan (extracted from *Saccharomyces*), Curcumin (extracted from *Curcuma longa*, one of the ingredients of Indian Curry), Resveratrol (extracted from grape), and Epicatechin gallate (extracted from Green Tea) (CCREg) is used in the form of a vaginal spray which, thanks to its formulation, can create a protective film that can favour the process of reepithelization, together with antioxidant, anti-inflammatory and antitumoral effects. Carboxy-methyl-beta-glucan promotes improved re-epithelialization and the synthesis of a mucoprotective film against bacterial and viral agents [15]. Curcumin has antioxidant, anti-inflammatory, and free radical-neutralizing actions. Isolated use of Curcumin, due to its liposolubility and rapid metabolism, reduced its therapeutic efficacy [16-17]. Only use as a basic cream on the cervical mucosa provided initial regression of cervical carcinoma [18]. The *in vivo* and *in vitro* therapeutic efficacy of Curcumin can be enhanced by synergistic mechanism using two other water-soluble phenols Resveratrol and Epicatechin gallate (CREg)(TriCurin). Resveratrol belongs to the polyphenol family and has an antioxidant effect capable of neutralizing free radicals produced by oxidation reactions responsible for cell damage followed by inflammation with related local infectious processes of both bacterial and viral nature (the latter responsible for preneoplastic lesions). Epicatechin gallate has effective antioxidant activity in eliminating free radicals, reduces ROS release, and has an immunostimulatory effect by reducing neoplastic growth [15, 19-21]. (**Table 1-3**).

Table 1. Natural history of CIN.

CIN	Patients n	Regression %	Persistence %	Progression to CIS %	Unvaried progression %
CIN 1	4,504	57	32	11	1
CIN 2	2,247	43	35	22	5
CIN3	767	32	<56	-	>12

Table 2. Vaginal Mixture used in spray formulation (CCREg).

	Origin	Mechanism of action
1. Carboxymethyl-beta-glucan (C) (Hydrophilic polymer)	Saccharomyces cerevisiae	<ul style="list-style-type: none"> • Improvement of reepithelization • Protective mucus film against bacterial and viral agents
2. Curcumin (C) (Polyphenol) C21H20O6	Plant origin: extracted from Curcuma longa	<ul style="list-style-type: none"> • Antioxidant • Anti-inflammatory • Neutralizes free radical
3. Resveratrol (R) (Polyphenol) C14H12O3	Plant origin: extracted from grapes and blueberries	<ul style="list-style-type: none"> • Antioxidant • Anti-inflammatory • Neutralizes free radicals
4. Epicatechin gallate (Eg) (Polyphenol) C22H18O10	Plant origin: extracted from green tea	<ul style="list-style-type: none"> • Antioxidant • Neutralizes free radicals • Reduces neoplastic growth

Table 3. Components of CCREg spray.

Components	
Carboxymethyl-beta-glucan (C)	110 mg
Curcumin (C)	40 mg
Resveratrol (R)	10mg
Epicatechin gallate (Eg)	120 mg

Table 4. Comparison between patients affected by CIN 1 undergoing therapy with CCREg and those who did not undergo treatment.

	Persistence of CIN1 at 6 months	Regression of CIN1 at 6 months	Total
Patients treated with CCREg	13 (28.9%)	32 (71.7%)	45
Control group	25 (55.5%)	20 (44.4%)	45

The study aims to evaluate the regression of HPV-related CIN1 after treatment with a vaginal mixture of Carboxymethyl glucan, Curcumin, Resveratrol, and Epicatechin gallate (CCREg) administered in a spray formulation for 6 months, compared to a control group of patients that did not undergo the treatment.

MATERIALS AND METHODS

95 patients presenting CIN1 referred to the Service of Lower Genital Tract Pathology of the Clinic of Obstetrics and Gynecology of the University of Perugia were considered; Inclusion criteria were patients with histological diagnosis of CIN 1, with satisfactory colposcopy (visible SCJ; absence of colpitis; trophic epithelium; well detectable cervix).

Exclusion criteria was patients who underwent an immune-suppressive therapy.

5 patients have been excluded by the study: 2 were undergoing an immune-suppressive therapy due to Lymphatic Leukemia and were scheduled for bone marrow transplant, one patient with AIDS undergoing antiretroviral therapy and 2 patients undergoing continuous corticosteroid therapy because of autoimmune diseases.

The age of the 90 patients examined ranged between 25 and 55 years of age; patients were divided into 3 groups according to their age (25-35 years; 36-45 years; 46-55 years).

The study included 90 patients presenting an LSIL-HPV PAP Test or HPV-related ASCUS, underwent colposcopy and cervical biopsy, with histological diagnosis of CIN1. Colposcopy has shown in all the patients a visible SCJ with “Abnormal colposcopic findings Grade 1 (minor) (ANTZ G1: Abnormal Transformation Zone Grade 1) (thin white epithelium and/or regular mosaic and/or regular punctate) or “non-acetowhite and non-uptake areas after Lugol’s staining”. The Bethesda 2014 Classification was used for the cytological diagnosis [22], the WHO 2020 classification for the histological report [23], and the IFCPR Rio De Janeiro 2011 classification for the colposcopic diagnosis [24].

The 90 patients examined have been divided into two groups: 45 “patients treated with CCREg” and 45 “untreated patients - control group”. We have then considered “regression and non-regression groups” among the “treated patients” and the “control group” according to the age division.

45 patients have undergone treatment with CCREg-based spray continuously for 6 months (one application in the evening – 5 puffs), while for the other 45 patients no treatment was done. Both groups underwent a PAP Test and an HPV Test after 6 months to evaluate the rate of regression or persistence of the lesion (Table 4).

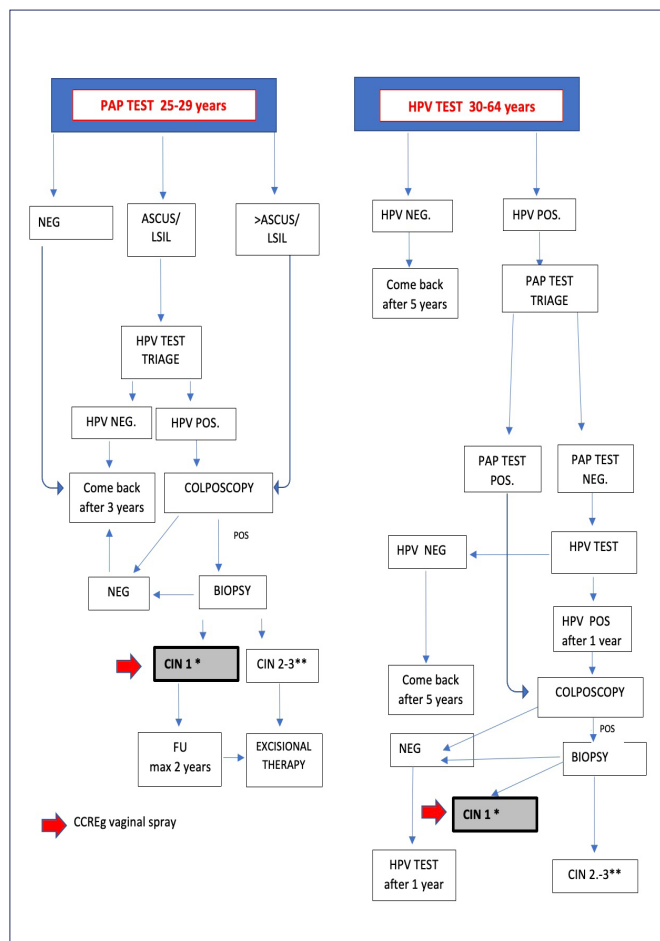


Figure 1. From “Cervical screening: two different pathways”.

A second-level textbook for the screening of cervical carcinoma, II Edition GISCI – SICPCV (modified).

All patients included belong to the Screening Program for Uterine Cervical Carcinoma. Diagnoses were performed on the “BD SurePath Liquid Based PAP -Test” thin-layer system and colposcopy examinations have been performed with “Zeiss Colposcope 150 FC”.

For patients aged between 25-29, the protocol (Figure 1) indicates a triage with HPV Test in case of ASCUS or LSIL PAP Test and, if positive, access to second-level investigation (colposcopy with biopsy); in case of negative HPV Test, patients are invited to come back after 3 years.

In patients aged between 30-64, a primary HPV Test is performed; in case of a negative HPV test, patients are invited to come back after 5 years. PAP Test is then conducted only in case of HPV-Test positivity and, if it results positive, the patient undergoes colposcopy. In case of a positive HPV Test and negative PAP Test, an annual follow-up is required; if the HPV Test results positive in two

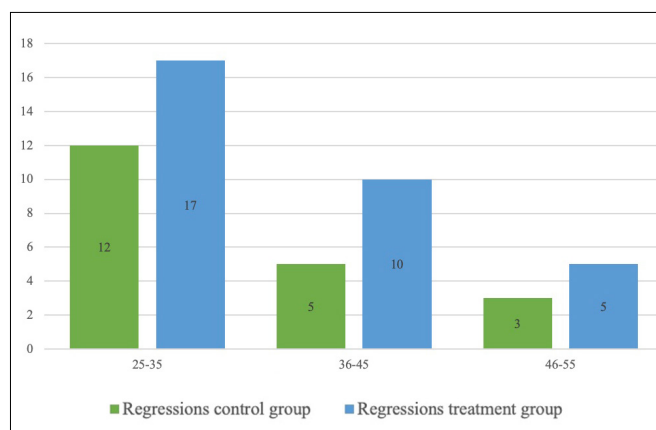


Figure 2. Age of patients who underwent or did not undergo the treatment with CCREg spray with regression of CIN 1.

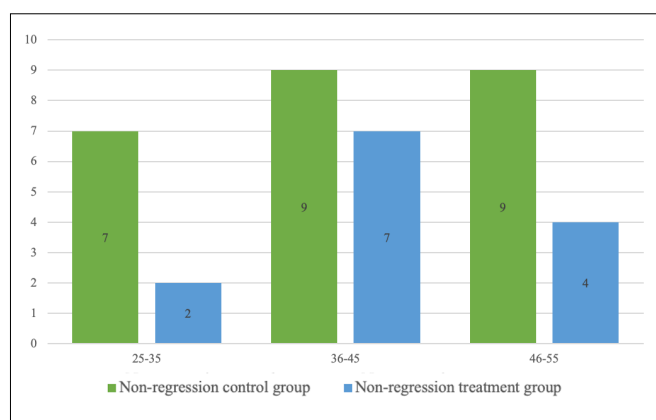


Figure 3. Age of patients who underwent or did not undergo the treatment with CCREg spray with persistence of CIN 1.

consecutive yearly checkups with a negative PAP Test, the patient is referred to second-level investigation. Cervical excisional therapy is indicated in case of CIN1 persistence during follow-ups for a period above 2 years from diagnosis and in case of CIN2-3.

RESULTS

The average age of the patients examined was 28 years.

At the end of the 6 months, patients treated with CCREg that presented a regression of the lesion were 32 (71.1%), while in the control group regression occurred in 20 cases (44.4%) (Table 4).

The number of patients treated with CCREg presenting with a persistent CIN1 was 13 (28.9%), while in the control group, the patients that didn't undergo regression were 25 (55.5%) (Table 4).

The main age group presenting a reduction of CIN1 among both treated and untreated patients is the one between 25-35 years of age (29 cases; 55.8%) (Figure 2).

The main age group presenting persistence of CIN1 in both treated and untreated patients is the one between 36-45 years of age (16 cases; 42.1%) (Figure 3).

The difference between the treated and the non-treated cases crosswise affects all age groups. In the group aged 25-35 years, the regression rate was 37.8% (17/45) in treated patients, compared to 26.7% (12/45) in control patients; in the group aged 36-45 years, the regression rate was 22.2% (10/45) in treated patients compared to 11.1% (5/45) in control patients; in the group aged 46-55 years, the regression rate was 11.1% (5/45) in treated patients compared to 6.6% (3/45) in control patients (Figure 2).

The non-regression rate of CIN 1, in the group aged 25-35 years, was 4.4% (2/45) in treated patients compared to 15.5% (7/45) in control patients; in the group aged 36-45 years was 15.6% (7/45) in treated patients compared to 20.0% (9/45) in control patients; in the group aged 46-55 years, it was 8.9% (4/45) in treatment patients compared to 20.0% (9/45) in control patients.

DISCUSSION

The management of Low-grade Intraepithelial Lesions (CIN1) involves monitoring the lesion by performing colposcopy, PAP test, and HPV test annually. The persistence of the lesion for some time longer than 2 years from diagnosis poses an indication for cervical conization treatment.

The spontaneous regression of the lesion is possible and is attributable to several factors, including the patient's age and immunocompetence, together with different factors (type of virus, vaginal microbiota, oxidative stress, etc.) that cannot be standardized [13, 21].

Although our study is limited by a small sample analysed and by strict inclusion criteria (histological diagnosis of CIN 1, with satisfactory colposcopy) that represented just a small side of HPV-affected population, has shown a significant regression rate in the patients that underwent the treatment 32/45 (71.1%) compared to the wait-and-see control group 20/25 (44.4%) that cannot be ignored and must be taken in consideration in the next following studies.

About our study, other limitations are represented by not considering immune status of patients (HPV vaccination), viral load, cervicovaginal microbiota, smoking habit.

A pharmacological approach already present when dealing with HPV is vaccination; a great number of studies have shown how HPV vaccination is very useful to prevent the infection and coinfection with multiple HR-HPV. Early HPV vaccination is fundamental to prevent recurrent HSIL after conization and is the only modifiable factor that slightly reduce the recurrence rate [25]. It must be done even in case of hysterectomy performed for high-grade lesions HPV related because it has shown a great efficacy to reduce the develop of lower genital tract dysplasia [26].

Carboxymethyl-beta-glucan, in the spray mixture under study, is a hydrophilic polymer capable of forming a micro-adhesive film on the vaginal mucosa that protects against infectious aggression from external microbial and viral agents and contributes to the maintenance and control of the physiological condition of the cervicovaginal mucosa through hydration, ensuring a physiological vaginal pH. Carboxymethyl-beta-glucan contributes to the maintenance and restoration of the vaginal microbiota through a probiotic effect ensuring positive effects on cervico-vaginal preneoplastic lesions. It was observed that patients on carboxy-methyl-beta glucan therapy, compared with the control group, had significant improvement in ectopia/ectropion and greater extent of metaplasia with relative maturation of cervical areas and mucosal uptake to Lugol. Lavitola *et al.* demonstrated that treatment with carboxy-methyl-beta-glucan resulted in significantly higher 6-month regression of histologic diagnosis of CIN 1 in the group with therapy (23.7%) than in the control group (6.8%).

In a multicentre study, the literature showed that the synergistic formulation of curcumin, Epicatechin gallate, and resveratrol (Tricurin), inhibited HPV E6, eliminated HPV+ tumour cells, and inhibited tumour progression [27].

Curcumin (from curry) (C) is very potent against Cervical Carcinoma Cells (CCC), but poor bioavailability due to reduced hydrophilicity has limited its clinical use.

Natural polyphenols such as Resveratrol (from grapes) (R) and Epicatechin Gallate (from Green Tea) (E) also show activity against Cervical Carci-

noma Cells (CCC). By treating CCC (HeLa) with Curcumin (C) or Epicatechin gallate (Eg) or Resveratrol (R) or a complete combination of these compounds, AA calculated the combination index and observed high synergism between C, Eg, and R at the unique molar ratio 4:1:12.5. This combination named Tricurin rapidly reduced the expression of HPV 18 E6 and NF- κ B while simultaneously inducing the tumour suppressor protein p53 in HeLa cells. In mice, the action caused by Tricurin was superior to that of Curcumin (4.7-fold for inhibition of E6 and 2-fold, 6-fold, and 1.7-fold for induction of p53, acetyl-p53, and active caspase-3, respectively).

Therefore, the synergism of the three natural principles was shown to be more potent in destroying TC-1 and HeLa cells of cervical carcinoma.

Perhaps, in the future, pharmacological treatment could represent a valid alternative to postpone or replace surgical treatment in case of low-grade lesions. In fact, surgical treatment has the advantage of being radical but also has disadvantages, especially when treating patients of fertile age; it is a clear risk of preterm delivery, lower birth weight and preterm premature rupture of membrane before 37 pregnancy weeks in surgical treated women when compared to untreated ones, especially with “cold knife conization” or “large loop excision of transformation zone” and it is also influenced by cone size, cervical length, repeated treatment and short conization-to-treatment interval [28, 29].

Future research could be oriented towards the search for a pharmacological treatment that is effective in all patients affected by low-grade HPV-related pathology, to provide a valid therapeutic alternative that allows us to perform surgeries only in highly selected patients. Future research should also be conducted considering previously mentioned biases.

CONCLUSIONS

Despite the fact that Low-grade Intraepithelial Cervical lesions require years before evolving into a frankly neoplastic pathology, guidelines suggesting an initial wait-and-see approach and these lesions possibly undergoing spontaneous regression, our study has highlighted how the application of adjuvant antitumoral treatment with

CCREg spray can favour a higher probability of regression of the lesions. Although the regression rate doesn't appear significative among the three age groups, it is evident that, according to data from the most recent literature, the highest regression rate takes place in the group aged 25-35, related to the high viral clearance that occurs mostly between 25-30 years of age [7].

Between the two age groups considered, there is a higher regression rate among the patients treated with CCREg, which has shown antitumoral properties attributable to therapeutic agents in support of CIN1 regression [22].

It can be concluded that the synergistic spray formulation usable on the cervical mucosa of Carboxy-methyl-beta-glucan, Curcumin, Resveratrol, and Epicatechin gallate (CCREg), is promising in the regression of low-grade preneoplastic lesions associated with HPV infections.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

A.B., M.T., L.A., F.S., L.F.C., S.G.: Conceptualization, investigation, methodology, resources, software, visualization. A.B., R.S., L.F.C., S.G.: Data curation. A.B., S.G.: Formal analysis. A.B., L.F.C., S.G.: Project administration, supervision, validation, writing – original draft, writing – review & editing.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests

Ethical approval

N/A.

Informed consent

The enrolled patients gave their informed consent to the study.

Data sharing

Data are available under reasonable request to the corresponding author.

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