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Open Access Article ***A Prospective Study***

Complementary Treatment with SILOffGyn after loop Electrosurgical excision of Cervical Intraepithelial Neoplasia CIN: a prospective study

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SUMMARY: This is a prospective study to assess a complementary treatment for CIN after loop electrosurgical excision procedure (LEEP). Ninety one patients were enrolled in two randomized groups: A1: LEEPalone. A2: LEEP, followed by SILOffGyn for 3 months. Pap smears repeated one year after the initial procedure showed that SILOffGyn marginally prevented CIN persistence or recurrence: 53, 3 % versus 46, 7 % (trend but non–significant difference:N.S.). Despite the N.S. difference, this complementary treatment seems to have some efficiency and could be proposed as anadditional measure to preventrecurrence after LEEP for CIN. Studies with greater number of patients and a longer period of follow-up could confirm our preliminary results.

INTRODUCTION

Background

Loop electrosurgical excision procedure (LEEP) (1) used alone or in combination with other procedures and/or pharmacological agents (PA) decreases the risk of recurrence of cervical intraepithelial neoplasia. Curcumin (2) (diferulolylmethane, 1,7 (4-OH-3 methoxy phenyl) 1–6, heptadene 3,5-dione) is included among the mentioned PA. Curcumin, an active ingredient of Indian spice is derived from the herb Curcuma and used extensively for cooking in south-east Asian

region. Besides its use as a spice, it has innumerable health effects with antiviral, anticancer (Bano et al 2018, Khan et al 2018) (3,4), anti-inflammatory (Moutinho et al 2018) (5), antioxidant, chemopreventive and wound healing properties, when used alone or in combination with other agents. As a dietary supplement, it has been shown to be a pharmacologically safe compound with almost no side effects. Curcumin has antiangiogenic effects and it can suppress cell growth and tumor formation by different routes, including the induction of apoptosis via mitochondrial pathways activation. Actually, curcumin has been demonstrated to inhibit carcinogenesis of murine skin, stomach, intestine and liver (Cheng et al 2001) (6). However, the toxicology, pharmacokinetics and biologically effective doses of curcuminin humans have not been extensively studied.In vitro studies in cervical dysplasia cells have shown that curcumin has a strong anti-HPV effect. Similarly, clinical data showed that the intravaginal application of a curcumin-based vaginal cream at bed time for 4 weeks resulted in remarkable clearance of HPV. Actually, curcumin inhibits the transcription of HPV 16: E6/E7 as early as 6 hours post-treatment, restoring the expression of tumor suppressor proteins including p53 and Rb. However, although curcumin, among others, down regulates HPV oncogene expression and serves as a potential therapeutic agent for HPV-induced cancers, its hydrophobicity, rapid metabolism, and poor bioavailability are some of its major disadvantages. Therefore, some other agents were attached to curcuminin an effort to circumvent these problems. A recent study by Angelova(7) showed that patients with HPV genital infection whose lesions have been preliminarily treated with this agent showed relatively faster improvement and healing (Angelova et al 2016).In conclusion, it appears that this natural herbal may serve as a strong anti-HPV agent, which can be used for the prevention of HPV infection or facilitate the effective treatment of cervical neoplasias by targeting and sensitizing neoplastic cells.

Aim of the study

This is a prospective study to assess if a complementary treatment with a curcumin product (SiLOffGyn) after LEEP for CIN decreases the rate of recurrence and increase the percentage of HPV clearance.

MATERIALS AND METHODS

This prospective study was conducted in Rea Hospital in Athens. Ninety one patients (aged 20-62 years, mean age 37 years) with CIN were included in the study. Mean time from first sexual intercourse and mean number of Pap smears until CINdiagnosis was of 18 (years) and of 16 (smears) respectively. Baseline demographics of the above patients are seen in the results. The patients were recruited from a total of 118 women. Recruitment period started in 2017 and ended in august 2019, Any previous pharmaceutical treatments were included in the exclusion criteria 27 patients were excluded from the study because they reported at least one previous therapeutic procedure, or the control PAP test was not done , delayed or the patient was lost.

Patients were eligible if they had CINdiagnosed for the first time and not as a recurrence; and did not receive any previous treatment. As this is a preliminary study, no power calculation of the appropriate sample size was conducted and «all available» patients were included in the study.

All patients were treated with LEEP: Loop Electrosurgical Excision Procedure *(Figure 1) & (Figure 2)*. The procedure was performed by gynecologists of Rea Hospital specialized in colposcopy and cervical surgery.

In the study group of patients we complete the surgical treatment with a local intravaginal cream SilOffGyn CE 0373, GEL 30ml containing the follow ingredients: Curcumin, Docosanol, Emblica officinalis, Aloe vera, Polidocanol,Glyceryl laurate, fat acids V12-20/8 OE, imidazolinidyl, urea, sodium dehydroacetate. The mode of application was in the patients after the LEEP: one vaginal application during six consecutive days and the next weeks one vaginal application twice a week during 6 months.

Depending on the further treatment, patients were randomly subdivided in 2 groups: drawing letters A1 :surgical treatment with LEEP alone or A2 : surgical treatment with LEEP followed by treatment with the cream SiLOffGyn : A1 with 41 (45,1%) patients and A2 with 50 (54,9%) patients. After the therapeutic procedure, patients belonging to the group A2 received all an additional treatment with SiLOffGyn for 6 months as mentioned before . Clinical and colposcopic examination was repeated at 12 weeks intervals and a final examination within 12 months was made for all the patients (with a maximum of 3 examinations for each patient). Assessors were blinded to the patient's treatment allocation.

A regulatory approval and written consents were obtained from the Scientific Hospitals' Committee and participants respectively. There was no funding for the trial. For the purpose of this study the chi square method was used through a SPSS

20 program. A p value higher than 0,05 was considered significant.

RESULTS

The mean number of sexual partners was 3 (range 1-6), a history of oral contraception was recorded in 13 (14,3%) patients and heavy smoking (more than 10 cigarettes per day) was reported by 38 (41,8%) patients.

Cytological and/or colposcopic disappearance of CIN and HPV was diagnosed in 35 cases (46,7 %) of group A1 and 40 cases (53, 3 %) of group A2, without clinical recurrence and PAP test within 12 months from initial evaluation: showing a trend of increased efficacy of SilOffGyn (Table 1) . No adverse effects were reported in group A2 patients,only 5 patients complained about a slight itching a few minutes after the application of the cream, no one stop the treatment and in the majority of the patients (89%), the itching disappear after a few weeks. The chi square method reveals that there is no statistical significance between the use of SilOffGyn and the negative cytological results, even though the is a difference in percentages **(p=0, 5)** (Table 2).

A marginal statistical difference (N.S.) was found comparing groups A1 and A2, which could be attributed to small numbers. Thus, a possible beneficial effect should not be excluded taking into account the obvious difference in percentages. In addition, shorter time of cytological remission was concluded in group A2 patients as for 21 patients of group A2 and 18 patients of group A1. Although it was not possible to determine the exact time of remission in the above cases, this ranged between 16 and 24 weeks (time between first and second examination and Pap Test).

DISCUSSION

Loop excision of the transformation zone has proved an efficient procedure for CIN treatment with therapeutic results similar to hysterectomy (Kang 2001)(8). Compared with similar conservative methods, as cryotherapy, LEEP was associated with a significantly lower risk of persistence and recurrence of CIN.The previous conclusions could wane the real efficacy of different agents on CIN recurrence with the argument that LEEP is already strongly efficacious for a permanent therapeutic result. On the other hand, although there is no doubt that HPV related lesions possess a remarkable potential for spontaneous regression, if left untreated, the synergistic action of some agents proved beneficial. As an example, treatment with Polimod and vitamin C, after laser vaporization of HPV related genital warts was efficient in decreasing the rate of recurrences (Zervoudis, Iatrakis et al 2010)(9). Similarly, the synergistic action of curcumin can be proved beneficial. Actually, curcumin, as a single agent or in combination with other substances(Mukherjee et al 2018)(10) has antiviral, anticancer, anti-inflammatory, antioxidant, chemopreventive and wound healing properties. If we take into consideration the above–mentioned data, a permanent regression of CIN lesions could be hypothesized after treatment with curcumin related products. Considering that HPV lesions recur frequently after treatment, a complementary treatment should be considered to reduce the percentage of recurrences. Although LEEP, implies high therapeutic rates of CIN lesions(11)(12), the «restoration» healing process could be accelerated with curcumin products.

Even though our study did not include other lab evaluations (except of Pap smears), the beneficial results of SiLOffGyn in our patients, were «undisputed».

The efficacy of SiLOffgyn was previously shown in similar lesions with a good safety profile. Although, our results could be impaired from other co–factors (like a better initial immunologic status of group A2), a possible beneficial effect of SiLOffGyn on CIN lesions could not be excluded. Furthermore, the similarity of ages, number of sexual partners and smoking among groupsconfirms that these characteristics did not impair the final findings. Further studies with increased number of patients could clarify the possible beneficial action of SiLOffGyn in CIN lesions.

CONCLUSION

Treatment with SiLOffGyn, after LEEP for CIN lesions could be efficient in decreasing the rate of recurrences. If this beneficial effect was confirmed in further studies, it could be attributed to the fact that the combined action of curcumin and similar substances, probably increases the natural defense and decreases persistence of cytologic abnormalities. Further studies with more cases should be encouraged, in order to assess complementary systemic treatments after LEEPfor CIN, due to the moderate or high rate of recurrences.

Conflicts of Interest: The author declares no conflicts of interest regarding the publication of this paper.

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*Table 1. Groups * PAP test after 1 year Crosstabulation*

		PAP TEST AFTER1 YEAR		Total
		NEGATIVE	POSITIVE	
group treated with loop and siloffgyn	Count	40	10	50
	% within V1	80,0%	20,0%	100,0%
	% within PAP TEST AFTER1 YEAR	53,3%	62,5%	54,9%
	% of Total	44,0%	11,0%	54,9%
group treated loop	Count	35	6	41
	% within V1	85,4%	14,6%	100,0%
	% within PAP TEST AFTER1 YEAR	46,7%	37,5%	45,1%
	% of Total	38,5%	6,6%	45,1%

Total	Count	75	16	91
	% within V1	82,4%	17,6%	100,0%
	% within PAP TEST AFTER1 YEAR	100,0%	100,0%	100,0%
	% of Total	82,4%	17,6%	100,0%

Table 2. Chi square test

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	,448[a]	1	,503		
Continuity Correction[b]	,154	1	,695		
Likelihood Ratio	,453	1	,501		
Fisher's Exact Test				,587	,350
Linear-by-Linear Association	,443	1	,506		
N of Valid Cases	91				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 7,21.
b. Computed only for a 2x2 table

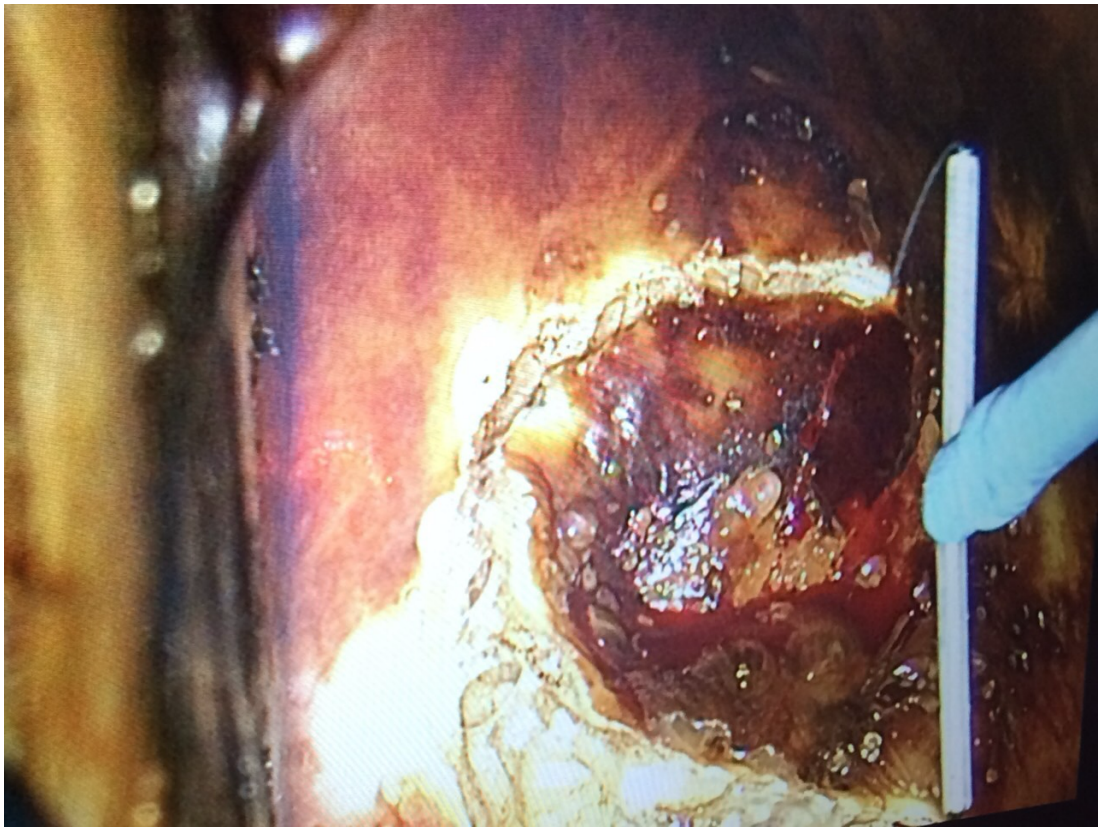

Figure 1: LEEP procedure: cutting with the Loop.

Figure 2: LEEP procedure: end of the procedure with Monsel cream