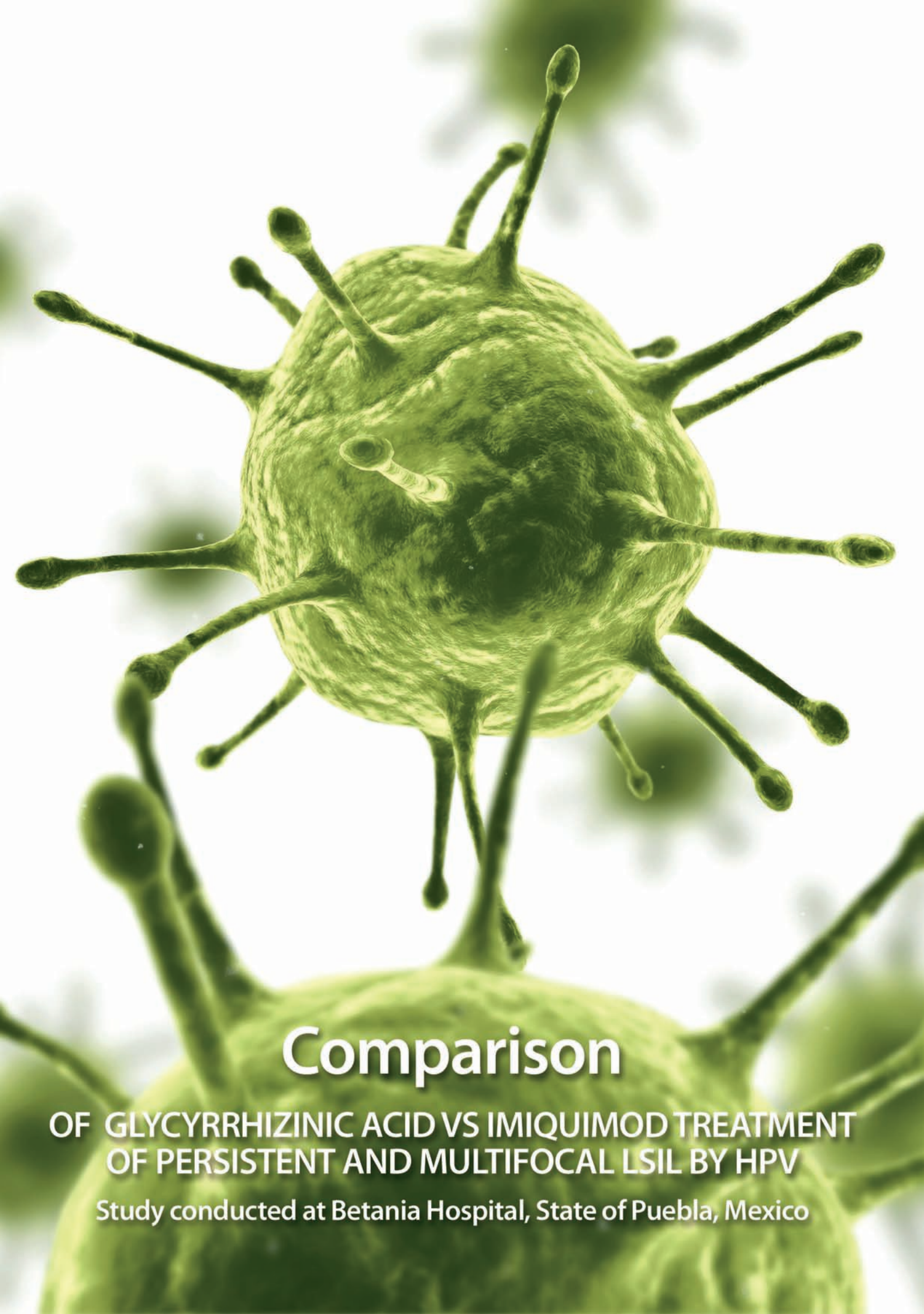

Comparison

OF GLYCYRRHIZINIC ACID VS IMIQUIMOD TREATMENT OF PERSISTENT AND MULTIFOCAL LSIL BY HPV

Study conducted at Betania Hospital, State of Puebla, Mexico

COMPARISON OF ACID GLYCYRRHIZINIC VS IMIQUIMOD TREATMENT OF PERSISTENT AND MULTIFOCAL LSIL BY HPV

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ABSTRACT

BACKGROUND:
At present, infection with human papillomavirus (HPV) is a public health problem in the world.

OBJECTIVES:
To compare the clinical efficacy and safety, as well as local and systemic adverse effects of glycyrrhizinic acid vs Imiquimod in patients ISSSTEP dysplasia clinic of hospital diagnosed with multifocal persistent LSIL.

MATERIAL AND METHODS:
Prospective, longitudinal, open, comparative, observational study.
We selected patients with a diagnosis of multifocal persistent LSIL openly assigning them into two groups with glycyrrhizinic acid 54 and 29 with imiquimod for the period July 2012 to June 2013. Variables of age, location of lesions, colposcopy and histology results, decrease or disappearance of lesions, adverse effects were used.
Means, percentages with IBM SPSS 22.0 and comparative analysis was performed using Student's t statistical program were analyzed.

RESULTS:
83 patients were included in the study with ages of 20 and 70.
Local adverse effects were reported with imiquimod 62% (T: 1.9) vs glycyrrhizinic acid 7% (T: 1.3) and systemic adverse effects with imiquimod 38% (T: 1.6), larger colposcopic improvement with glycyrrhizinic acid 20% (T: 1.7) vs 14% imiquimod (T: 92) greater histological improvement with 57% glycyrrhizinic acid (T: 2.4) vs 18% imiquimod (T: 1.17).

CONCLUSIONS:
est colposcopic and histological results and fewer side effects with glycyrrhizinic acid compared imiquimod are reported.

Background.

The oncogenic human papillomaviruses were discovered in 1989; since then, it has become apparent that the human papillomavirus (HPV) is the causative agent of cervical cancer. This idea got professor Harald Zur Hausen,(1)

The human papillomavirus (HPV) is a large group of viruses. More than 100 different types have been identified, almost 40 of these are sexually transmitted and infect the male and female genital tract. Out of these, there are at least 15 types that are considered to be high-risk (produce cancer). Types 16 and 18 are associated with cervical cancer, and types 6 and 11 are linked with benign lesions, such as acuminata.(2)

The most common high-risk human papillomaviruses in the world are found in Africa and Latin America (the most frequent virus types are HPV 16, 18, 31, 35, 39, 45, 51, 52, 56 and 58). Out of all these, the most prevalent in Latin America is the HPV-16. In Central and South America, the high-risk viruses HPV-33, HPV-39 and HPV-59. (1,2)

S·nchez-Alem·n and co-workers reported a 14.4% prevalence of HPV in a study carried out on Mexican university students with one or more sexual partners.(3)

Studies carried out in the United States have demonstrated that around 1% of the sexually active population has genital warts; 4% of the population could have HPV lesions if they were studied by means of the colposcopy; nearly 10% of the population would be HPV positive even though they had a negative colposcopy; and finally, 60% of the population might have detectable antibodies in their organism, which would indicate that at a certain moment in time they had been exposed to some type of human papillomavirus.

Biology of HPV

HPV belongs to five of the 18 genera of the Papillomaviridae family: alpha, beta, gamma, mu and nu. The papillomavirus are characterised for being small non-enveloped virus that are between 45 nm and 55 nm in diameter, with one icosahedral capsid protein.(4-8)

Its double-stranded circular deoxyribonucleic acid genome (DNA) of approximately 8,000 base pairs in length, and one icosahedral capsid made up of 72 capsomers produced from two structural proteins that do not have a nuclear membrane, contain nine or 10 coding regions, known as open reading frames (ORF's).(4,8)

The viral DNA has eight genes, of which six codify for early proteins (E) and two for late proteins (L). The proteins E5, E6 and E7 are involved in the neoplastic transformation, and E1 and E2 in the replication of the viral genome; moreover, E2 regulates the early gene expression and, in particular, it inhibits theexpressionofE6andE7 oncogenes. The genes L1 and L2 codify for the capsid proteins.(2)

The viral transforming genes E6/E7 are responsible for the loss of control of the cellular proliferation. Studies carried out on cell cultures have demonstrated that the E6/E7 transforming genes are complementary and when only one is expressed, its transforming power is very weak. These genes are more frequently expressed in the high-risk viral types such as 16 and 18, and their expression is not observed in the low-risk types such as 6 and 11.(4)

Standard treatment options for cervical SIL: Currently, the conventional methods include the so-called local destructive treatment (LDT) and the excisional therapy. The LDT used are physical: electrocoagulation and cryotherapy. These methods are most frequently used on the low-grade SIL.(8)

Excisional therapy includes the electrosurgical excisional procedures (radiosurgery), laser and cold-knifeconization, which are popular in the treatment of high-grade SIL.(8)

They are all intended to remove the lesion but not the infection caused by HPV. They do not prevent relapses either: this type of excisional procedure can trigger off or help increase the morbidity that could affect the women's reproductive capacity. For this reason, we set out to find a reliable and safe alternative for the treatment of these patients.

The main objective is to compare the efficacy and the safety of using glycyrrhizinic acid vs. Imiquimod in patients diagnosed with low-grade persistent multifocal squamous intraepithelial lesions caused by HPV.

Material and methods

Prospective, linear, open-label, comparative and observational clinical trial. A search was carried out for patients with persistent, multifocal, cervical, vaginal and vulvar low-grade SIL at the Dysplasia Clinic Service of the Maternity Infant Unit at the Specialities Hospital ISSSTEP from June 2012 to June 2013, which had not cleared up on its own or despite having previous excisional and/or ablative surgery.

All the patients were diagnosed by means of a cytology, colposcopy and histology test; they were being treated at the Dysplasia Clinic Service of the Maternity Infant Unit at the Specialities Hospital ISSSTEP and they satisfied the inclusion criteria of this clinical trial.

Having recruited the patients, two open-label groups were then formed for our study.

Following the masking procedure, the patients diagnosed with low-grade persistent multifocal squamous intraepitheliallesions were randomly selected and assigned to two groups: Imiquimod and glycyrrhizinic acid.

54 patients were assigned to the group that was given glycyrrhizinic acid and 29 patients were assigned to the group that was given Imiquimod.

To obtain the information, medical records were compiled that focused on identifying risk factors associated with the development of cervical cancer, a colposcopy was carried out and the corresponding report was stored on a computer file, and an initial colpocytogram was completed.

It was used personal laptop, computer used by the Dysplasia Clinic Service, sheets of bond paper, cotton buds, acetic acid, Lugol's iodine, Monsel's solution, gloves, procedure masks, vaginal mirrors, cotton balls, colposcope, digital camera, colposcopic image capture system, Cytobrush, Papette spatula, pathology laboratory, Imiquimod (medication included in the basic drug list of the Specialities Hospital ISSSTEP), and glycyrrhizinic acid spray medicine (provided by MEDIX laboratories).

The following variables were used as a way to determine the response to the treatment: age, site of lesion, results of colposcopy and histology, decrease or disappearance of the lesions, toxicity, erythema, edema, ulceration, infection, necrosis and rash.

All the patients were evaluated before the treatment started to make sure that they satisfied the recruitment criteria. This was carried out at a unit equipped especially for this purpose which was run by a PhD student and/or the consultant. A questionnaire was filled in and a physical examination to find any signs of adverse reactions and to determine the aforementioned clinical variables was carried out.

The evaluation was carried out when the established treatment period was over. In the final evaluation, a colposcopy was carried out and the biopsy sample was taken.

The cytologic and histological tests were carried out by the Anatomical Pathology Department that gave the diagnosis of the initial biopsy and the final post-treatment biopsy.

The treatment regimen in the two groups under analysis administered Imiquimod and glycyrrhizinic acid was followed as established in table 1.

The response criteria were established according to the following parameters: colposcopic and histological results. In each evaluation of the aforesaid parameters, the following response criteria was defined:

- Complete response (CR)
- Partial response (PR)
- Disease stable (DS)
- Progressive disease (PD)

TABLE: 1

Medication	*Imiquimod*	*Glycyrrhizinic acid*
Presentation	Cream sachet (250 mg)	Spray bottle containing 60 ml of the solution.
Formula	Imiquimod (12.5 mg)	50.0% propylene glycol, 49.0% water, 0.9% polysorbate 80, 0.1% glycyrrhizinic acid
Route of Administration	Topical	Topical
Application	Applied using the speculoscopy procedure at the unit by a healthcare professional, 2 times a week for 8 weeks.	Intravaginal application carried out by the patient with 2 squirts of the solution on the vaginal fornix and the middle 1/3 of the vagina and/or 1 squirt on the vulva (in vaginal and cervical lesions it is applied through the vaginal canal; in vulvar lesions the device is used externally), 3 times a day for 2 weeks initially or up to 6 weeks if need be.

The statistical analysis was carried out with the IBM SPSS 22.0 statistics software, Windows version. The mean values and percentages were assessed, and the comparative analysis was carried out using the Student's t-test.

RESULTS

83 patients were included in the study with age limits of 20 and 70 years, 54 patients in the glycyrrhizinic acid group and 29 patients in the Imiquimod group.

IMIQUIMOD

The subjects with the highest incidence of HPV in the group that was given Imiquimod were aged 41-50 (9= 32%), 31-40 (8= 29%), 51-60 (6= 21%) and 61-70 (3= 11%).

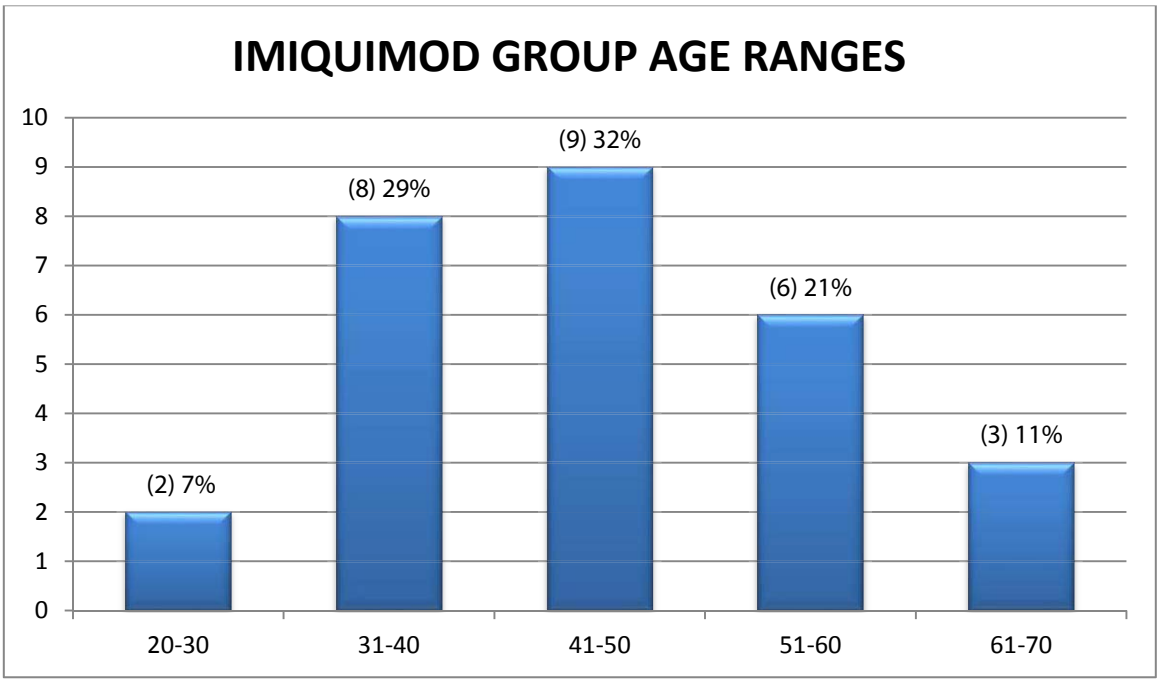
The most frequent lesion sites were the cervix-vagina-vaginal fornix (9) 32%, cervix-vagina (6) 21%, cervix-vaginal fornix (4) 14%, cervix-vagina-vulva (3) 11%, cervix (2), vagina-vulva (2), vault-vagina (2) 7%, respectively.

The colposcopic results were: PR (5) 18%, CR (4) 14%, DS (3) 11%.

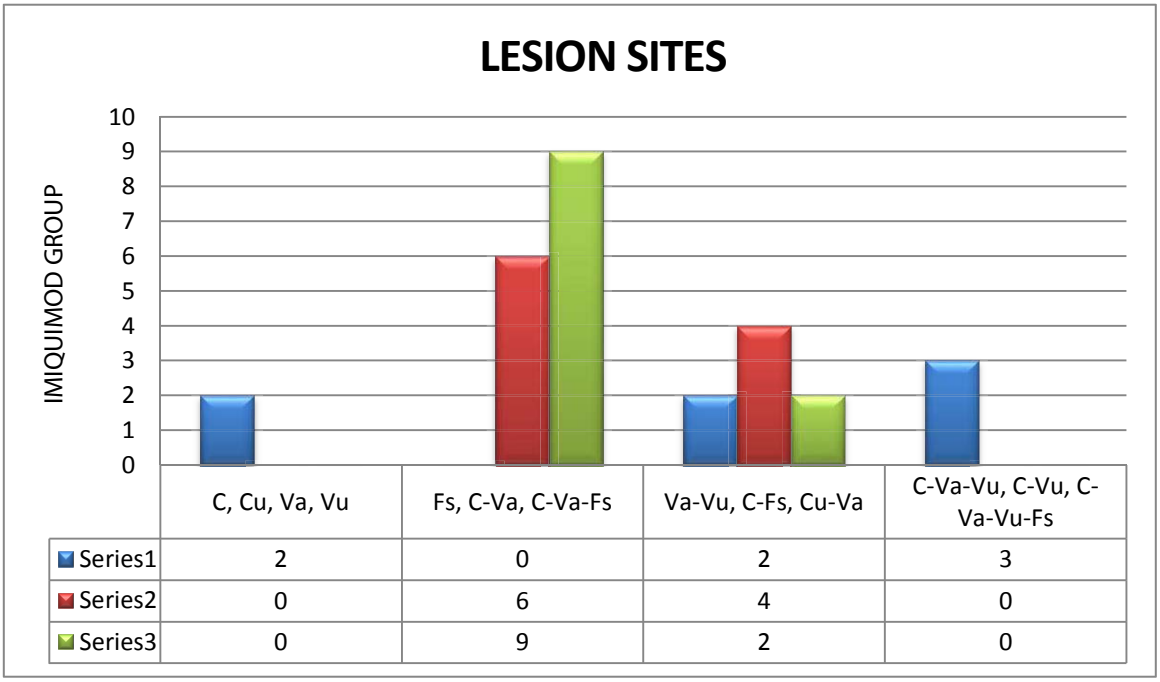
The histological results were: PR (1) 3%, CR (5) 18%, DS (6) 22%.

The rest of the patients dropped out of the clinical trial (16) 57%.

GRAPH 1



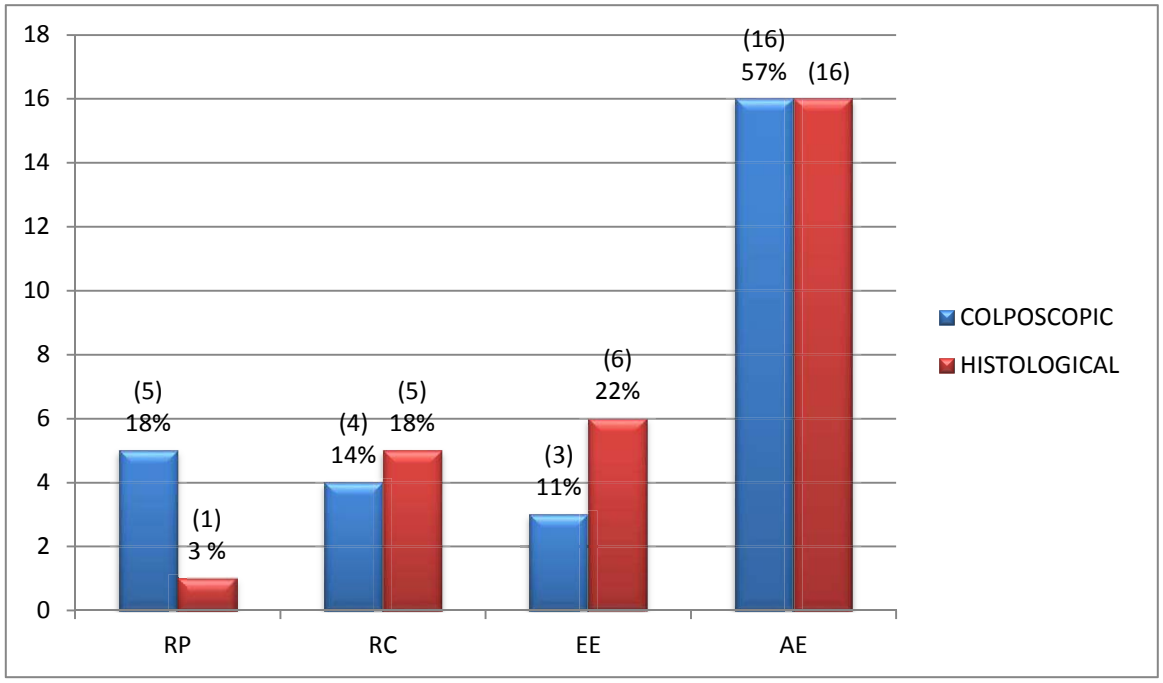
GRAPH 2



	C, Cu, Va, Vu	Fs, C-Va, C-Va-Fs	Va-Vu, C-Fs, Cu-Va	C-Va-Vu, C-Vu, C-Va-Vu-Fs
Series1	2	0	2	3
Series2	0	6	4	0
Series3	0	9	2	0

C: Cervix, Cu: Vault, Va: Vagina, Vu: Vulva, Fs: Vaginal fornix

GRAPH 3 **IMIQUIMOD GROUP RESULTS**



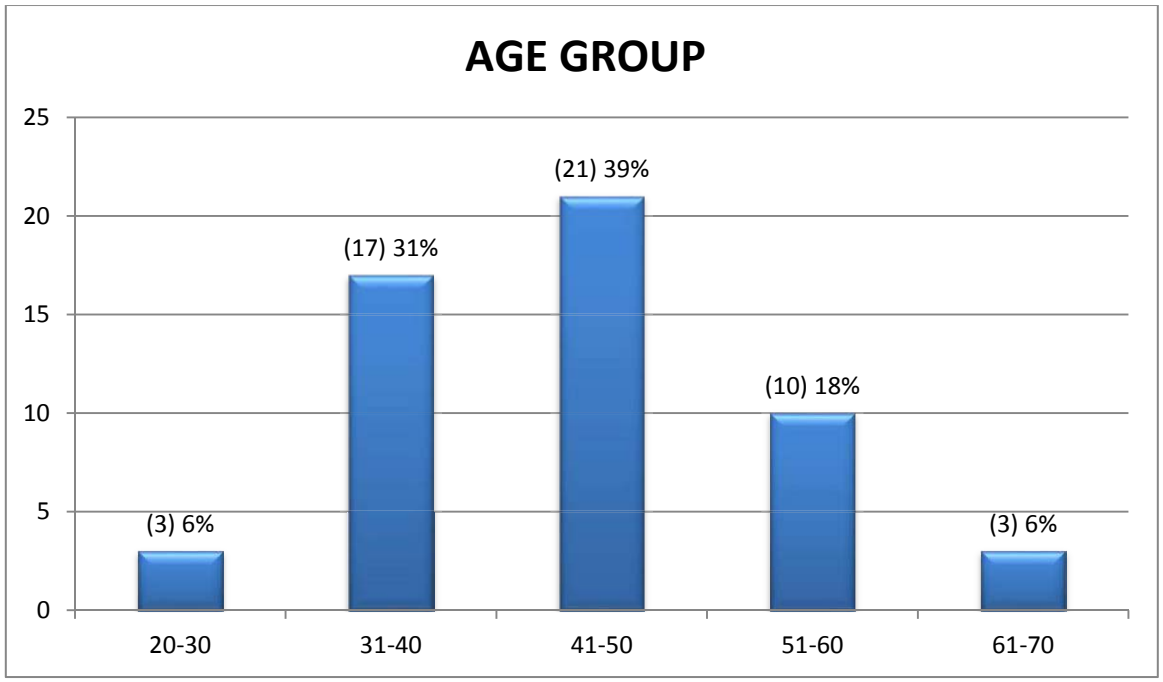
PR: PARTIAL REMISSION
DS: DISEASE STABLE

CR: COMPLETE REMISSION
AS: ABANDON STUDY

GLYCYRRHIZINIC ACID

The incidence per age group in the group that was given glycyrrhizinic acid was: 41-50 (21) 39%, 31-40 (17) 31%, 51-60 (10) 18%, 20-30 (3) 6% and 61-70 (3) 6%.

GRAPH 4 **GLYCYRRHIZINIC ACID AGE GROUP**

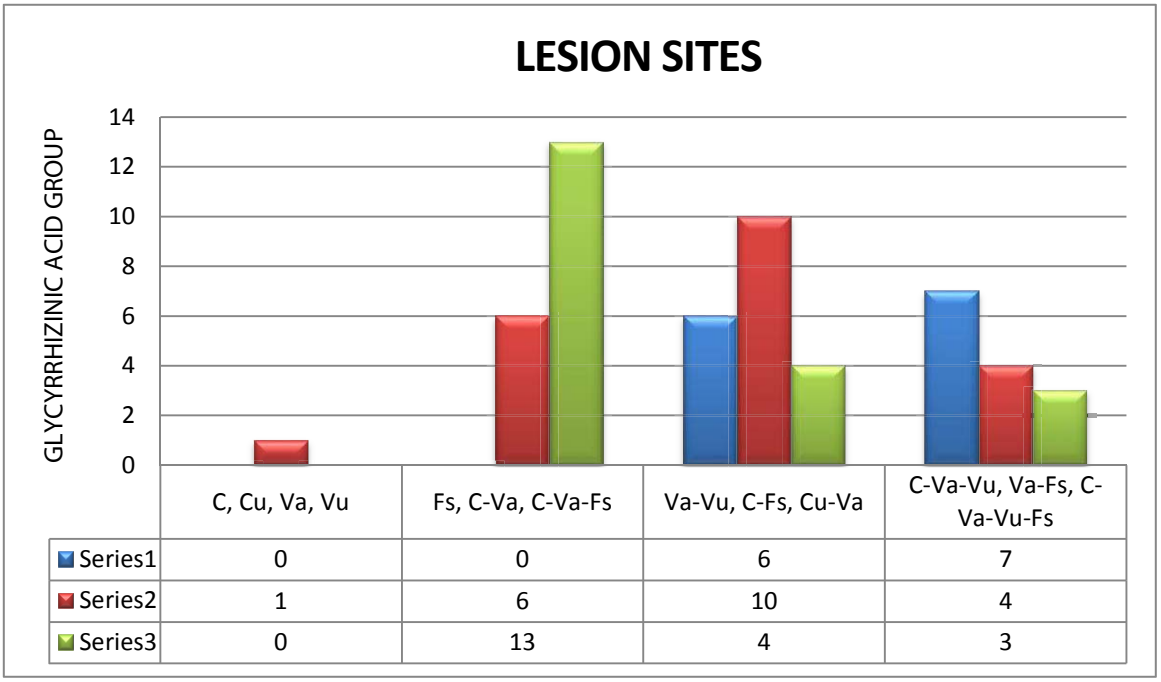


The most frequent lesion sites were: cervix-vagina-vaginal fornix (13) 26%, cervix-vaginal fornix (10) 18%, cervix-vagina-vulva (7) 13%, cervix-vagina (6) 12%, vagina-vulva (6) 12%, vault-vagina (4) 7%, vagina-vaginal fornix (4) 7%, vault (1) 5%.

The colposcopic results were PR (29) 54%, CR (11) 20%, DS (14) 26%, PD (0) 0%.
The histological results were: PR (0) 0%, CR (31) 57%, DS (23) 43%, DP (0) 0%.

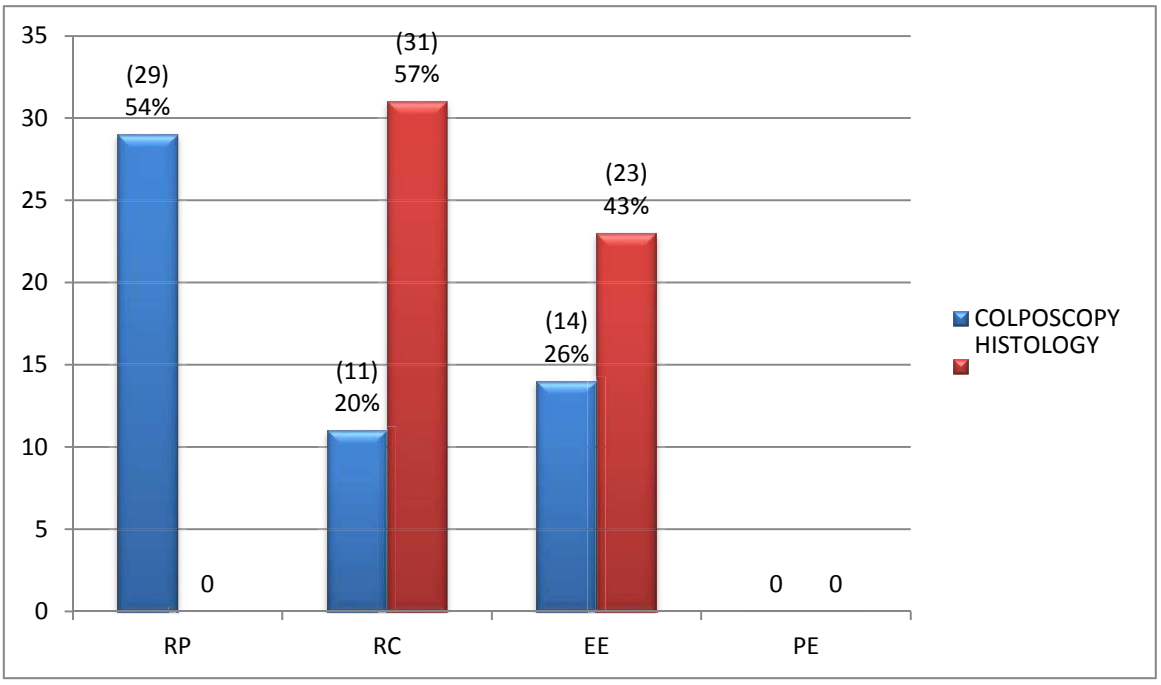
The local and systemic adverse events of the medications were recorded in the following way: local Imiquimod (18) 62% vs. glycyrrhizinic acid (4) 7%, systemic adverse effect Imiquimod (11) 38% vs. glycyrrhizinic acid 0%, no adverse effect Imiquimod 0% vs. glycyrrhizinic acid (50) 93%.

GRAPH 5 **GLYCYRRHIZINIC ACID GROUP LESION SITE**



C: Cervix, Cu: Vault, Va: Vagina, Vu: Vulva, Fs: Vaginal fornix

GRAPH 6 **GLYCYRRHIZINIC ACID GROUP RESULTS**



PR: PARTIAL REMISSION
DS: DISEASE STABLE

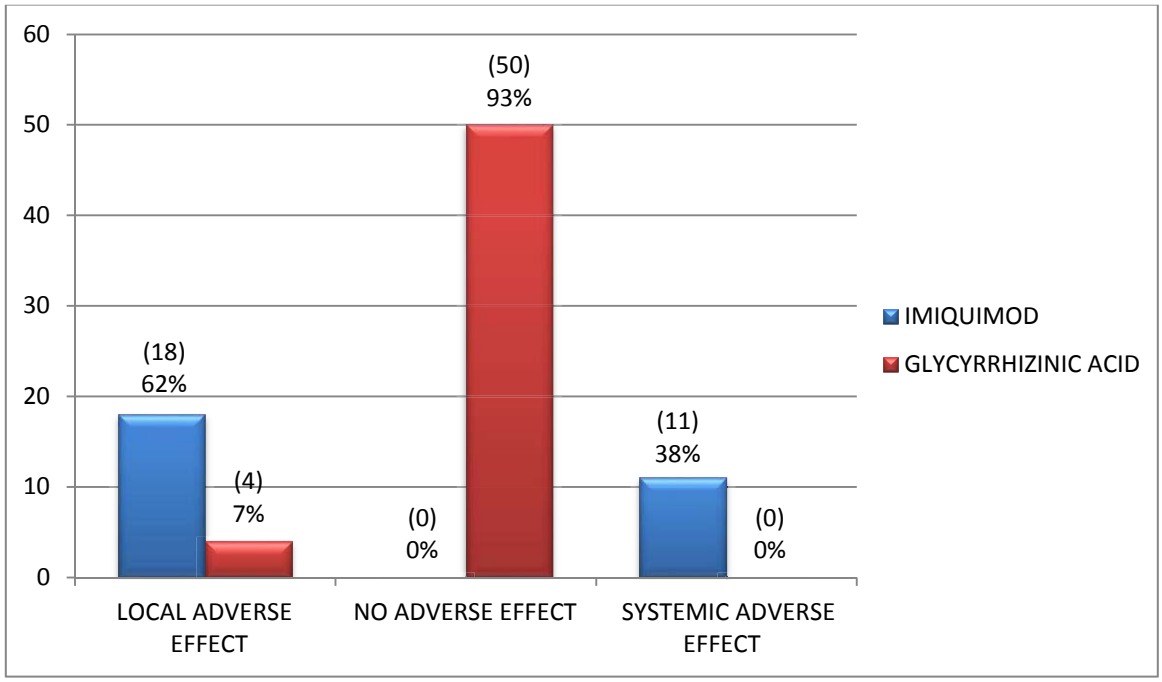
CR: COMPLETE REMISSION
PD: PROGRESSIVE DISEASE

Local adverse effects were reported with Imiquimod 62%, (T: 1.9) vs. glycyrrhizinic acid 7% (T: 1.3) and systemic adverse effects were reported with Imiquimod 38% (T: 1.6).

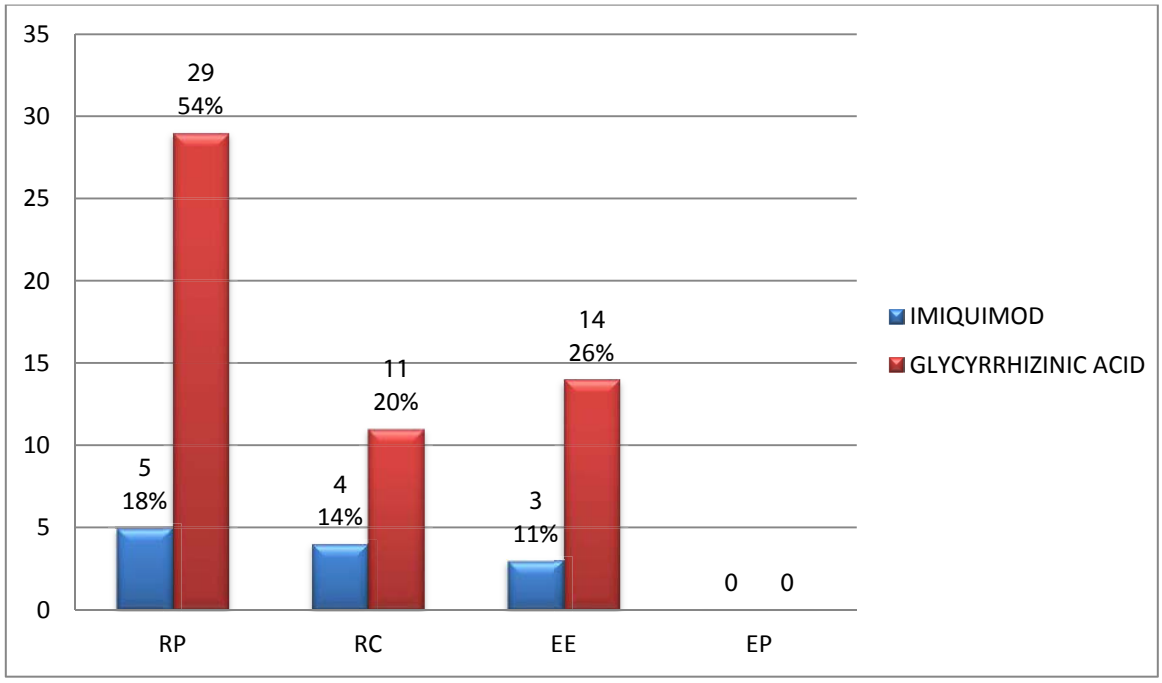
The colposcopic improvement is greater with glycyrrhizinic acid 20% (T: 1.7) vs. Imiquimod 14% (T: .92).

The histological improvement is greater with glycyrrhizinic acid 57% (T: 2.4) vs. Imiquimod 18% (T: 1.17).

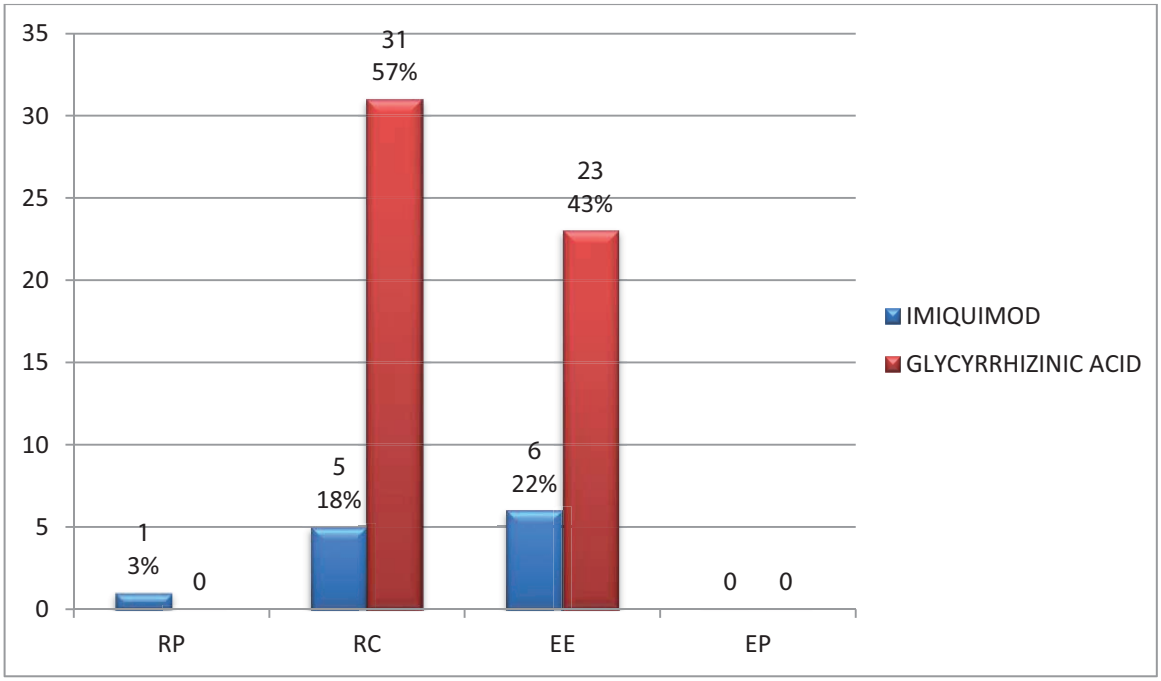
GRAPH 7
COMPARISON OF ADVERSE EFFECTS CAUSED BY GLYCYRRHIZINIC ACID VS IMIQUIMOD



GRAPH 8 **COMPARISON OF THE COLPOSCOPIC RESULTS**



GRAPH 9 COMPARISON OF THE HISTOLOGICAL RESULTS



Dscusion

Currently, an effective and non-invasive treatment has been sought that offers beneficial results and at an affordable cost for the management of infections and injuries caused by the human papilloma virus.

A variety of different treatment modalities have been used in the past in an attempt to avoid the use of radical procedures.

While 5% imiquimod cream has been widely used for the treatment of condylomata acuminata of the vulva, in recent years reports have been reported with a small number of patients using it for the treatment of high-grade vulvar intraepithelial neoplasia (VIN 2/3) with acceptable disease regression rates.

The rationale for this type of therapy is based on the conjecture that multicenter lesions of the lower genital tract are strongly related to HPV.

Therapy by topical application of Imiquimod could be a potential alternative treatment method, but it should not be considered as permanent.

In previous studies, carried out in countries such as Spain and Russia, where women with condylomatous lesions or with signs and symptoms of human papillomavirus infection in the urogenital route were studied, the diagnosis in both cases was established with the reaction method to lapolimerase, and to whom activated glycyrrhizinic acid was administered.

The treatment carried out was the application of activated glycyrrhizinic acid to the injured area. In general, after 7 to 10 days of treatment or 2 to 4 procedures, complete clinical recovery was observed.

In a study carried out in Mexico, it is concluded that activated glycyrrhizinic acid has high antiviral efficacy against the human papilloma virus, demonstrated in the short-term evaluation. The continuity of its activity, after 20 days of having concluded the treatment, is a relevant characteristic; however, cases of cytological positivity may be due to infection, especially in individuals with an active sexual life.

The results of this study are consistent with those reported so far and carried out with the same methodology. Therapeutic failures can be attributed to errors in drug administration.

Conclusions

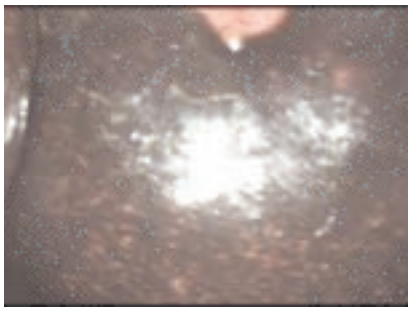
Better colposcopic and histological results were reported in the experimental group given glycyrrhizinic acid compared with the results obtained by the experimental group given Imiquimod.

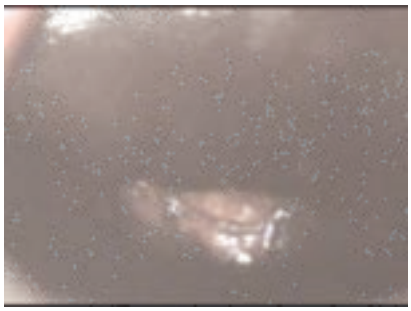
Furthermore, in the comparative analysis less adverse effects were observed in the group that was given glycyrrhizinic acid compared with those experienced by the subjects from the group given Imiquimod.

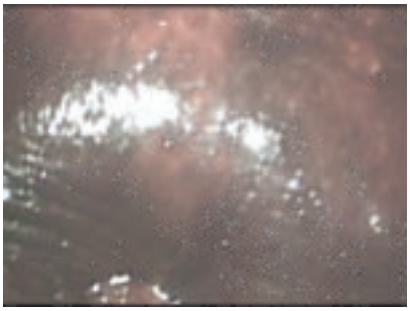
The results obtained are in line with those reported in related literature.

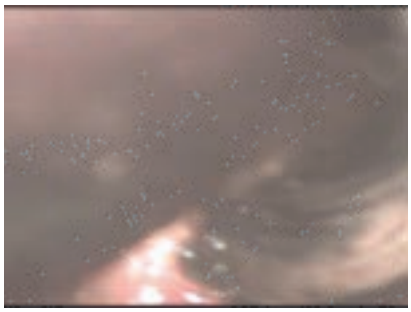
Our clinical trial universe proves that glycyrrhizinic acid is therefore an ideal medication to treat low-grade, persistent, multifocal squamous intraepithelial lesions and less adverse reactions are experienced with this product.

The conclusion drawn is that the medical treatment with glycyrrhizinic acid is an ideal alternative to avoid surgery to remove the lesions.









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