



# Focal multiepithelial hyperplasia: comparative treatment, glycyrrhizinic acid versus liquid nitrogen

## *Hiperplasia multiepitelial focal: tratamiento comparativo, ácido glicirricínico contra nitrógeno líquido*

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### ABSTRACT

In pediatric population, focal multiepithelial hyperplasia (FMH) is characterized by the onset of multiple lesions in the mucosa of the mouth; it is associated to the human papillomavirus. Presently, no special treatment is preferred, the most widely used is liquid nitrogen (LN) treatment, nevertheless, this is an uncomfortable and painful treatment for the patient. This would prompt us to look for new, less invasive treatment alternatives such as use of glycyrrhizinic acid (GA). **Aim:** To compare GA efficiency versus LN in FMH in Mexico Children's Hospital patients (HIM) aged 5 to 13 years. To determine clinical epidemiological characteristics as well as adverse effects. **Material and methods:** The present was a randomized controlled clinical trial. It was divided into two groups: group A was treated with GA applications, four times a day, two atomizer shots, for one month. Group B was treated with LN once a month for three months. **Results:** 20 pediatric-age patients were studied, out of which 11 were male and 9 female. 12 patients had relatives afflicted with the disease. Most frequent topography was the lower lip. Efficiency of group treated with GA was 63% when compared to group treated with LN which exhibited 81% efficiency. Systemic diverse effects were only observed with use of LN. 0.075 p was obtained (7.5%). **Conclusions:** GA efficiency was ascertained although it was lesser than that of LN. GA can be used as an adjuvant treatment in order to decrease lesions, it elicits minimal local adverse effects.

### RESUMEN

La hiperplasia multiepitelial focal (HMF), se caracteriza por la aparición de lesiones múltiples en la mucosa de la cavidad bucal en población pediátrica y se asocia con la presencia del virus papiloma humano. Actualmente no existe un tratamiento de elección, el más empleado es el nitrógeno líquido (NL), pero es doloroso e incómodo para el paciente. Es por eso la necesidad de buscar nuevas alternativas de tratamiento, tratando de ser menos invasivos, como el ácido glicirricínico (AG). **Objetivo:** Comparar la eficacia del AG contra el NL en la HMF en pacientes entre los 5 a 13 años de edad, en el HIM. Determinar las características clínico-epidemiológicas y los efectos adversos. **Material y métodos:** Ensayo clínico controlado aleatorizado. Se dividió en dos grupos. Grupo A tratado con la aplicación de AG cuatro veces al día con dos disparos del atomizador por un mes. Un grupo B tratado con NL una vez al mes por tres meses. **Resultados:** Se estudiaron 20 pacientes en edad pediátrica, 11 masculinos y 9 femeninos; 12 con familiares afectados. La topografía más frecuente fue el labio inferior. El grupo tratado con AG tuvo una eficacia de 63% en comparación con NL que tuvo una eficacia del 81%. Sólo se observaron efectos adversos sistémicos con NL. Se obtuvo una p de 0.075 (7.5%). **Conclusiones:** Se comprobó la eficacia del AG, a pesar que fue menor que con NL. Se puede utilizar como un tratamiento coadyuvante para disminuir las lesiones, con mínimos efectos adversos locales.

**Key words:** Focal multiepithelial hyperplasia, glycyrrhizinic acid, liquid nitrogen.

**Palabras clave:** Hiperplasia multiepitelial focal, ácido glicirricínico, nitrógeno líquido.

### INTRODUCTION

Focal multiepithelial hyperplasia is considered an infrequent condition, nevertheless, in the last 10 years, it has increased in our environment. Dr. Archard, in 1965 first introduced the term focal multiepithelial hyperplasia to describe oral lesions observed in certain indigenous groups native of New Mexico. Papillomavirus is involved in this process: genotypes 13 and 32 are the most frequently detected with DNA *in situ* hybridization techniques, although HPV cross reactions have also been described.<sup>1-3</sup>

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Genetic factors have equally been associated, as well as malnutrition, poor hygiene and poverty. From the clinical standpoint, this process is characterized by the presence of multiple papular lesions in the lower lip, buccal mucosa or tongue. Lesions are of a small size and color similar to that of surrounding mucosa. Histological picture is onset of parakeratosis, acanthosis with epithelial projections which anastomose horizontally and habitually koilocytes as well as other cellular changes indicating viral infection. Differential diagnosis must be undertaken with condylomata acuminata, oral florid papillomatosis, Cowden's syndrome and Crohn's disease.<sup>1-3</sup> Although there are reports stating that this condition exhibits a tendency to spontaneous regression, it can persist for years and thus inordinately worry the parents of the child, probably due to the esthetic problem and thus cause psycho-social repercussions in the child.<sup>4</sup> Up to this date, preferred treatment is liquid nitrogen application, which has proven to be quite painful; therefore, it would be necessary to find another treatment alternative, such as use of glycyrrhizinic acid, which can be considered a non invasive, non traumatic treatment, with lack of adverse collateral effects reported. Glycyrrhizinic acid (GA) is one of the components of the aqueous extract of the root of *Glycyrrhiza glabra* L root. This substance has been used in traditional medicine for its anti-inflammatory properties, it is better known as licorice. One molecule of glycyrrhizinic acid and two molecules of glucuronic acid form glycyrrhizin, a saponin also found in the aqueous extract of *G. glabra*. Biological actions of both composites, glycyrrhizinic acid and glycyrrhizin have been widely studied, and antiviral interferon-induction effects have been reported as well as anti-ulcerative and anti-inflammatory effects. Drs Pompei et al<sup>5</sup> demonstrated that glycyrrhizinic acid inhibits viral replication and cytopathological effects produced in cellular cultures by the following viruses: vaccine virus (Vv), type I herpes simplex virus (HSV-I), Newcastle disease virus (NDV) and vesicular stomatitis virus (VSV), but it had no effect on poliovirus 1 (PV). They equally observed that glycyrrhizinic acid irreversibly inactivated herpes simplex virus particles. Other researchers have reported *in vitro* antiviral activity of glycyrrhizinic acid against viruses of varicella zoster (VZ), human immunodeficiency (HIV) and hepatitis B. It has been observed that glycyrrhizin bonds to I P viral kinase and renders it inactive. Therefore it is believed that it interferes with the early stages of viral replication, preventing absorption of viral particles into the cell surface, or the virion exit from its capsid, and thus, its penetration into the cell.

In acute toxicology studies performed in rats, it was found that intra-peritoneal administration of high dosages of up to 2.5 g/kg did not cause mortality after 14 days' observation, neither did it cause significant lesions in organs or tissues.<sup>5-8</sup>

## OBJECTIVE

To compare efficiency of glycyrrhizinic acid versus liquid nitrogen in focal multiepithelial hyperplasia in patients aged 5-13 years at the «Federico Gómez» Children's Hospital in Mexico City.

## METHOD

Pediatric patients aged 5-13 years were admitted into the test. Patients were of both genders and had been diagnosed with focal multiepithelial hyperplasia. Patients did not exhibit concurrent systemic diseases. Patients were randomly distributed into two groups: group A was treated with glycyrrhizinic acid, with local application, twice a day, two atomizations, during four weeks. Group B was treated with liquid nitrogen: one local application, once a month, for three months. All cases were assessed through iconographic control and one written assessment of adverse effects through signs and symptoms. Group A was assessed once a week and group B once a month, until completion of treatment.

Lesion assessment was subjectively conducted, by comparing the initial photograph with the final one. The researcher visually analyzed all photographs, involving in the study a special computer program (Photoshop 7.0). In this program, all images were digitalized until equivalent proportions of each one were obtained; they were then subjected to morphometric analysis, where each square received a value of one square millimeter. Squares encompassing each of the patient's lesions were counted, to later obtain equivalence in percentages. Upon completion of the study, a second result was obtained when the photograph was once more examined. Based upon these data, percentages of lesion disappearance could be obtained.

## RESULTS

Out of a total of 20 patients 11 were male and 9 female; they were divided into two groups. Most frequent lesion location was the lower lip. The group receiving GA encompassed 6 males and 4 females, the group receiving LN comprised 5 males and 5 females. Patients were grouped according to age rank, thus 10 patients were in the 5-8 year group

**Table I.** Comparison between glycyrrhizinic acid and liquid nitrogen.

Patient	Lesions at onset	Final lesions	% Improvement	Effectiveness
Glycyrrhizinic acid				
M/7	10	0	100	Excellent
F/8	12	0	100	Excellent
M/11	12	3	75	Moderate
F/9	19	6	68	Moderate
F/7	15	6	60	Moderate
F/5	11	5	55	Moderate
M/6	21	10	52	Moderate
F/12	29	14	52	Moderate
F/5	31	20	35	Mild
M/8	21	14	33	Mild
Liquid nitrogen				
M/6	12	0	100	Excellent
M/8	18	0	100	Excellent
M/8	14	0	100	Excellent
F/10	19	3	84	Excellent
F/11	28	2	93	Excellent
M/11	33	0	100	Excellent
F/11	20	10	50	Moderate
F/9	29	10	66	Moderate
M/13	29	9	69	Moderate
F/9	15	7	53	Moderate



**Figure 1.** Papular lesion of the tongue.

and 10 patients in the 9-12 year age group. Only one patient was > 12 years. 12 patients had afflicted family members and 8 patients did not (*Table I*). Treatment success was assessed through the percentage of lesion disappearance, as observed in the final photograph. The following scale was used: 0% = no disappearance, 1-25% = minimal disappearance, 25-50% mild disappearance, 51-75% moderate, 76-



**Figure 2.** Papular lesions in lower lip.



**Figure 3.** Papular lesions in oral mucosa.



**Figure 4.** Treatment with liquid nitrogen.



**Figure 5.** Treatment with glycyrrhizinic acid.

**Table II.** Effectiveness: comparison between GA and LN.

Effectiveness	Glycyrrhizinic acid	Liquid nitrogen	Total
Excellent	2	6	8
Moderate	6	4	10
Mild	2	0	2
Total	10	10	20
Average	63%	81%	

100% = excellent disappearance. Observed clinical improvement was as follows: in the group treated with GA, at treatment completion, 2 patients (20%) exhibited excellent result, with total disappearance of lesions, 6 patients (60%) showed moderate results, 2 patients (20%) revealed light improvement in lesions (*Figures 1 to 3*). In the group treated with LN, at treatment completion, the following was observed: 6 patients (60%) exhibited excellent results, with total disappearance of lesions, 4 patients (40%) showed moderate results (*Figures 4 to 6*). GA exhibited 63% efficiency, compared with LN which showed 81% efficiency (*Table II*). Only 3 patients exhibited adverse effects (local erythema) in the GA group, on the other hand, patients of LN group presented erythema, edema, and pain. Only patients in this group exhibited nausea, vomit, and systemic adverse effects.

Student T test for independent samples was applied, the following was obtained:  $T = -1.88$ , this corresponds to  $p = 0.075$  (7.5%). Therefore, we can conclude that there is no statistically significant difference suggesting that glycyrrhizinic acid is better than liquid nitrogen.

## DISCUSSION

Prevalence rate of this popular disorder of the oral mucosa varies from 7 to 13% in susceptible population

and over 25% of these patients might have another family member afflicted with the same disease. Lesion biopsy and clinical manifestations<sup>8</sup> are the main diagnostic contributions. Cryotherapy is presently the most used therapeutic method, it has been used with favorable results, but, invariably, the pain caused prevents proper follow up and in many cases, causes patient desertion from the treatment.<sup>10,12</sup>

In this disease, several studies have reported presence of infection due to human papilloma virus (HPV), types 13 and 32, this has been achieved through viral DNA detection by techniques of Hybridization and polymerase chain reaction (PCR) in most studied cases.<sup>1,4,12</sup> Electronic microscopy studies revealed crystalloid-complexion viral particles within the nucleus.<sup>6,9,12</sup> The following can be found within the realm of differential diagnoses that must be proposed with focal multiepithelial hyperplasia: common warts, condyloma acuminatum, sponge nevus, oral white, oral mucosa leukoedema, Cowden's syndrome and squamous papilloma.<sup>7,6,11</sup> The following techniques have been used as therapeutic options: electrosurgery, electrofulguration and laser. All the aforementioned methods involve patient sedation, and can cause local adverse effects such as edema, erythema and pain. For these reasons, new treatment alternatives must be sought, such as use of aqueous presentation of Linn glycyrrhiza glabra root, or glycyrrhizinic acid. This root is traditionally known for its anti-inflammatory properties, presently, its anti-viral activities against many viruses are also known, since it prevents DNA and RNA replication in early phases. It equally prevents the virion's exit from its capsid, and thus its penetration into the cells. GA does not exhibit local or systemic adverse effects. The present is the first clinical essay where this new medication has been successfully used for treatment of focal multiepithelial hyperplasia. It has been based on previous research where GA was used for treatment of condyloma acuminatum, where suitable results and absence of adverse effects in patients had been observed.<sup>5-7</sup>

## CONCLUSIONS

Focal epithelial hyperplasia is a disease afflicting our population. Many treatments are used to combat it, but they entail several adverse effects, mainly pain. It is therefore necessary to find a treatment that can be efficient, economical and free of secondary effects. It has been demonstrated that glycyrrhizinic acid prevents viral replication in HPV cases. In the present study it

was possible to confirm the beneficial effects of this medication, nevertheless it could not be statistically proven that GA would exert greater effect than liquid nitrogen, since results obtained were rather similar. GA entailed certain advantages such as: ease of application, lesser treatment time and lack of adverse effects, contrary to liquid nitrogen treatment which entailed pain, local anesthesia for application as well as undesirable adverse effects for the patient. Further study is suggested in projects which might entail not only the same characteristics but also a longer follow-up period.

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