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EVALUATION OF THE TREATMENT OF RADIOPAQUE KIDNEY LITHIASIS THROUGH THE COMBINATION OF EXTRACORPOREAL LITHOTRICIA BY SHOCK WAVES AND FAGOLITOS PLUS®. PRELIMINARY CASE - CONTROL STUDY

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Summary.- *INTRODUCTION: The nutritional supplement called Fagolitos Plus® contains hydroxycitric acid as main component, in addition to zinc, magnesium, vitamin A and vitamin B6. It is necessary to study new molecules as chemolytic treatment in calcium lithiasis or that facilitate its fragmentation with the help of other instrumental treatments.*

OBJECTIVE: The objective of this study is to evaluate the effectiveness of the combined treatment of Fagolitos Plus® and extracorporeal lithotripsy in the fragmentation of the lithiasis.

MATERIAL AND METHODS: Retrospective case-control study includes 88 patients with lithiasis. Group1: Treated with 1 session of extracorporeal lithotripsy and Fagolitos Plus®. Group 2: Treated with 1 session of extracorporeal lithotripsy. The variables analyzed were: Age, sex, body mass index, maximum diameter of the stone, area of the stone, hounsfield units of the stone measured by axial tomography, location of the stone, result after 1 session of extracorporeal wave lithotripsy. shock [complete fragmentation, partial fragmentation (presence of a fragment greater than 5 mm) and absence of fragmentation (same size of the lithiasis)], adverse effects that occurred after taking Fagolitos Plus®, days of treatment with Fagolitos Plus® and energy shock wave applied to lithiasis. Results were analyzed with SPSS 20.0, p≤0.05.

RESULTS: The mean age of the patients included in the study is 53.81 ± 12.62 years in group 1 compared to 56.53 ± 12.37 years in group 2, p=0.31. According to the distribution by sex, there were no statistically significant differences (p=0.5), including 24 men and 24 women in group 1 and 23 men and 17 women in group 2. The mean of body mass index of the patients in group 1 was 28.39 ± 2.27 kg/m2 in group 1 versus 28.39 ± 3.03 kg/m2 in group 2, p=0.9. The maximum diameter of the stone was 11.5 ± 3.91 mm in group 1 compared to 13.15 ± 5.49 mm in group 2, p=0.1. The area of the lithiasis measured by tomography was 104.74 ± 70.56 mm2 in group 1 compared to 141.91 ± 80.95 mm2 in group 2, p=0.3. The Hounsfield units measured by tomography of the lithiasis in group 1 was 1061.98 ± 213.68 compared to 1143.15 ± 172.24 in group 2, p=0.06.

Relation to fragmentation, complete fragmentation was observed in 66.7% of group 1 patients, compared to 41% of group 2 patients (p=0.02), between 20-30 days after the first session of Extracorporeal Lithotripsy evaluated by means of a simple X-ray of the Abdomen.

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CONCLUSIONS: The administration of Fagolitos Plus® concomitant to extracorporeal lithotripsy could increase its effectiveness in lithiasis fragmentation, requiring clinical trials and prospective studies to confirm these findings.

Keywords: *Urinary lithiasis. Hydroxycitric acid. Lithiasic fragmentation. Extracorporeal lithotripsy by shock waves.*

INTRODUCTION

The medical treatment of urolithiasis is mainly focused on treating metabolic disorders with the aim of reducing recurrence in this type of patient. The European Urology Association's clinical guide has not undergone many changes in the last 10 years regarding medical treatment in these patients. It is still recommended treatment with thiazides and potassium citrate in patients with calcium lithiasis (calcium oxalate or calcium phosphate) as preventive treatment to avoid lithiasis recurrence or increased residual lithiasis by correcting metabolic abnormalities existing in the metabolic study, being useful in some cases the intake of supplements of magnesium, pyridoxine or hypouricemic agents (1-2). Currently, it only exists treatment focused on calculus for those of uric acid composition, to achieve chemolysis (1-2). Recently, a nutritional supplement called Fagolitos Plus® is being comercialized, (composed of 2069 mg of hydroxycitric acid, 200 mg magnesium, 25 mg vitamin B6, 10 mg zinc and 800 µg of vitamin A), which has in vitro properties, decreasing the mass of the calcium oxalate and calcium phosphate lithiasis (3), and it is not only focused on the treatment of calculus associated with other instrumental treatments, but also to avoid recurrence. In our usual clinical practice we use this product in patients with radiopaque lithiasis without active urinary infection and with high suspicion of calcium lithiasis, to control lithiasis recurrence, associated or not with other drugs and also as a complementary treatment to extracorporeal shock wave lithotripsy (ESWL).

The aim of this case-control study is to assess retrospectively and preliminarily the efficacy of Fagolitos Plus® as a complementary treatment after a ESWL session.

MATERIAL Y MÉTODOS

Type of study

- Retrospective case-control study in which 88 patients distributed in two groups are included:

- Group 1: 48 patients undergoing 1 session of ESWL and treatment with Fagolitos Plus® during 30 days.

- Group 2: 40 patients undergoing 1 session of ESWL.

In our usual clinical practice we evaluate the result of the ESWL session after 20-30 days of its performance, hence the treatment established with Fagolitos Plus® in these patients has been of an approximate duration of 30-40 days (starting 10 days before the ESWL session and continued until the next evaluation). The initial evaluation after the first ESWL session is performed with Abdomen X-ray and only in those cases in which fragmentation cannot be determined adequately Computerized Axial Tomography (CAT) is requested. The lithotripter used is the Gemini® (Dornier) shock wave electromagnetic system. The dosage used was 1 stick every 12 h.

- Inclusion criteria: Patients over 18 years without renal failure with lithiasis under 20 mm, radiopaque on abdominal radiography, with CAT study before the start of treatment with ESWL and without the presence of a demonstrated urinary tract infection by urine culture.

Exclusion criteria: Patients under 18 years, with active urinary infection or renal failure, with radiolucent or radiotransparent lithiasis.

Analyzed variables:

In this study, the following variables are evaluated: Age, sex, body mass index (BMI), maximum diameter of the lithiasis, area of the lithiasis, Hounsfield Units (HU) of lithiasis measured by CAT scan, lithiasis location, result after 1 ESWL session [complete fragmentation, partial fragmentation (presence of a fragment over 5mm) and absence of fragmentation (same size of lithiasis)] and adverse effects occurring after intake of Fagolitos Plus®, days of treatment with Fagolitos Plus® shock wave energy applied to the lithiasis.

- **Statistical study**

A statistical study with SPSS 20.0 program applying Student's t distribution is carried out, in order to compare between cuantitative variables groups and Chi-squared test to evaluate cualitative variables. A statistical significance is considered when $p \leq 0,05$.

- **Limitations of the study**

This is a retrospective study with a reduced number of patients, without randomization in the administration of the food supplement and not controlled. Selection and information biases may be incurred.

RESULTS

The mean age of the patients included in the study is 53.81 ± 12.62 years in group 1 versus at 56.53 ± 12.37 years in group 2, p = 0.31. According to the distribution by sex, there are no differences statistically significant (p = 0.5), including 24 men and 24 women in group 1 and 23 men and 17 women in group 2. The mean BMI of the patients in group 1 was 28.39 ± 2.27 kg / m2 in group 1 versus 28.39 ± 3.03 kg / m2 in group 2, p = 0.9. The maximum diameter of the lithiasis was 11.5 ± 3.91 mm in group 1 versus 13.15 ± 5.49 mm in group 2, p = 0.1. The area of the lithiasis measured by CAT scan was 104.74 ± 70.56 mm2 in group 1 vs 141.91 ± 80.95 mm2 in group 2, p = 0.3. The measured HUs by CAT of the lithiasis in group 1 was 1061.98 ± 213.68 versus 1143.15 ± 172.24 in group 2, p = 0.06. Therefore, there are no significant differences in none of these pretreatment parameters, being able to consider homogeneous and comparable groups (Table I).

In group 1 , complete lithiasis fragmentation occurs in 32 patients (66.7%), partial fragmentation in 8 patients (16.7%) and absence of fragmentation in 8 patients (16.7%), while in group 2 complete fragmentation exists in 16 patients (41%), partial fragmentation in 16 patients (41%) and absence of fragmentation in 7 patients (18%), statistically significant result p = 0.02 (Table II). The patients in whom there was partial fragmentation of the lithiasis underwent a second ESWL session, those in which there was no fragmentation were scheduled for semi-rigid and / or flexible ureteroscopy . In the cases of complete fragmentation they were preventively treated with Fagolitos Plus® with a dose of 1 stick every 24h.

Characteristics of the patients included in the study.

	Grupo 1	**Grupo 2**
AGE (years)	53,81 ± 12,62	56,53 ± 12,37
BMI (kg/m^2)	28,39 ± 2,27	28,39 ± 3,03
Maximum diameter (mm)	11,5 ± 3,91	13,15 ± 5,49
Area (mm^2)	104,47 ± 70,56	141,91 ± 80,95
HU	1061,98 ± 213,68	1143, 15 ± 172,24

In cases of partial fragmentation where ESWL was performed, the dosage of 1 stick every 12 h was maintained and in those in which ureteroscopy was performed due to a non fragmentation it was decided not to continue with Fagolitos Plus 1 stick every 12 hours dosage . The average number of days of treatment with Fagolitos plus® in group 1 has been 34.3 ± 6.7 days during the first ESWL session. Regarding the energy applied to lithiasis, it was of 140.56 ± 25.14 Joules in group 1 compared to 139.38 ± 32.14 Joules in group 2, p = 0.4. In group 1, only 4 patients manifested the presence of mild nauseous sensation with some doses of Fagolitos plus®.

DISCUSSION

The nutritional supplement called Fagolitos Plus® is a combination of different compounds in which the main component is the hydroxycitric acid. This compound was identified in 1965 as an acid component of the Garcinia Cambogia fruit [4], with important in vitro properties, highlighting its ability to bind calcium in a similar way as it binds to citrate , inhibiting crystallization and also weakening the molecular bonding of the calcium oxalate and calcium phosphate crystals [2]. Moreover, in vitro studies have shown that hydroxycitrate is able to dissolve calcium oxalate crystals in a supersaturated solution. The fact that is excreted through human urine and is not metabolized results in the urinary pH not being modified, unlike what happens with citrate, which alkalizes urine [3,5-8].Along with hydroxycitrate, other components of this nutritional supplement such as pyridoxine have shown its usefulness in patients with hyperoxaluria to decrease the excretion of this promoter of crystallization [9]. Just like it happens with zinc, which in both preclinical and clinical conditions is related to the appearance of lithiasis when there is a deficit of it [10,11]. Vitamin A has proven in experimental animals and in humans to be a crystallization inhibitor in urine and low levels of this vitamin are associated with an increased risk of lithiasis formation [12] and regarding magnesium, it is a complement that is used in conjunction with other compounds to reduce lithogenic risk [13].

Experimental studies have shown the effect of hydroxycitrate in the crystallization of calcium oxalate lithiasis, as well as in its elimination, that is, a double effect both prophylactic and therapeutic [14-16]. In our case-control study a greater ability for lithiasis fragmentation with extracorporeal shock wave has been observed in those patients to whom Fagolitos plus® has been administered. We cannot compare with other in vivo studies because to date we do not know of other work carried out in patients with this food supplement, only in vitro studies. It is possible that the demonstrated in vitro effect of hydroxycitrate, together with the rest of the components, ease, along with the shock wave effect the weakening of molecular bonding bridges of the crystal and greater fragmentation occurs, taking into account that there is no difference in the study regarding the hardness of the stone measured by CAT scan or energy applied during the ESWL session. However, this statement is only a hypothesis that must be studied through the design of randomized clinical trials evaluating if the treatment of Fagolitos Plus® together with ESWL increases lithiasis fragmentation and makes this instrumental treatment more effective. Currently, our group works together with others in a Phase IV Clinical Trial to try to demonstrate the effectiveness of this supplement as adjuvant treatment together with extracorporeal lithotripsy in fragmentation of calcium lithiasis.

Table II. Results of lithiasic fragmentation after 1 session of Extracorporeal Shock Wave Lithotripsy.

	Full fragmentation	Partial fragmentation	No fragmentation
Group 1	32 (66,7%)	8 (16,7%)	8 (16,7%)
Group 2	16 (41%)	16 (41%)	7 (18%)

CONCLUSION

Although the use of this nutritional supplement with hydroxycitrate cannot be recommended systematically, in this preliminary study it is observed greater fragmentation of the lithiasis with ESWL in patients taking this product. It is necessary to confirm these findings by performing clinical trials.

BIBLIOGRAPHY and READINGS RECOMMENDED (* reading of interest and ** fundamental reading)

1. EAU Guidelines on Urolithiasis. 2020. https://uroweb.org/guideline/urolithiasis/

** 2. Lancina Martín JA, Salinas Casado J, Rodríguez-Miñón JL, González Enguita C. Tratamiento médico de la litiasis urinaria. Urol. Integr. Invest.; c2019. 29 p.

** 3. Kim D, Rimer JD, Asplin JR. Hydroxycitrate: a potential new therapy for calcium urolitiasis. Urolithiasis. 2019; 47: 311-320.

** 4. Lewis Y, Neelakantan S. Hydroxycitric acid—the principal acid in the fruits of Garcinia cambogia desr. Phytochemistry. 1965; 4: 619–625.

5. Chung J, Granja I, Taylor MG, Mpourmpakis G, Asplin JR, Rimer JD. Molecular modifiers reveal a mechanism of pathological crystal growth inhibition. Nature. 2016; 536(7617): 446-450.

6. Chung J, Taylor MG, Granja I, Asplin JR, Mpourmpakis G, Rimer JD. Factors differentiating the effectiveness of polyprotic acids as inhibitors of calcium oxalate crystallization in kidney stone disease. Cryst Growth Des. 2018; 18: 5617−5627.

7. Kyada A, Mansuri N, Patel P. In vitro investigation of some alternative therapeutic agents for antiurolithiatic activity. J Pharm Res. 2017; 11(8): 955-961.

8. Li M, Zhang J, Wang L, Wang B, Christine V. Putnis CV. Mechanisms of modulation of calcium phosphate pathological mineralization by mobile and immobile small-molecule inhibitors. J. Phys. Chem. B 2018; 122:1580−1587

9. Xu H, Zisman AL, Coe LF, Worcester EM. Kidney stones: an update on current pharmacological management and future directions. Expert Opin Pharmacother. 2013; 14: 435-47.

10. Tasian GE, Ross ME, Song L, Grundmeier RW, Massey J, Denburg MR et al. Dietary Zinc and Incident Calcium Kidney Stones in Adolescence. J Urol. 2017; 197: 1342-1348.

11. Negri AL. The role of zinc in urinary stone disease. J Urol. 2017; 197: 1342-1348.

12. Grases F, Garcia-Gonzalez R, Genestar R, Torres JJ, March JG. Vitamin A and urolitiasis. Clin Chim Acta. 1998; 269: 147-57.

13. Massey L. Magnesium therapy for nephrolithiasis. Magnes Res. 2005; 18: 123-6.

* 14. Chen WC, Chen HY, Lin WY, Yang YR, Tsai MY, Chen YH. Inhibitory effect of hydroxycitrate on calcium oxalate crystal formation in a Drosophila model. J Food Nutr Res. 2018; 6: 706-709.

15. Fan Q, Feng X, Hong X, Gong S, Tian J, Hou F et al. Garcinia cambogia extract removes calcium oxalate kidney stones in both genetic and non-genetic Drosophila models of nephrolithiasis. BioRxiv. 2018; 27: 1-28.

* 16. Kyada A, Mansuri N, Patel P. Protective effect of magnesium lactate gluconate and Garcinia cambogia fruit extract in experimentally induced renal calculi in rats. J Intercult Ethnopharmacol 2017; 6: 378-384.