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Journal of Urology and Research

Research Article

Clinical Investigation of *Levisticum officinale* (Lovage) Effectiveness' in Patients with Cystinuria

MehrdadMohammadi[1,2], Erfan Parvaneh[2], and Zahra Tolou-Ghamari[1,2]*

[1]Department of Urology, Isfahan University of Medical Sciences, Iran
[2]Alzahra Research Centers, Isfahan University of Medical Sciences, Iran

*Corresponding author
Zahra Tolou Ghamari, Isfahan Kidney Transplantation Research Center, Alzahra Research Centers, Isfahan University of Medical Sciences, Isfahan/I.R. Iran, Tel: 98-3137922591; Email: toloeghamari@pharm.mui.ac.ir

Submitted: 28 September 2016

Accepted: 02 October 2016

Published: 04 October 2016

ISSN: 2379-951X

Keywords

- Levisticum officinale
- Cystine
- Cratinine
- Cystinuria
- Litolytic
- Nephroprotective

Abstract

Objective: According to previous publications, the erratic hereditary disease with the augmented urinary excretion of cystine, could be envisage as the key to major injury in complicated patients due to recurrent of kidney stones. Therefore, the aim of this study was to investigate the safety and efficacy of Levisticum officinale (Lovage) in patients with cystinuria

Patients and methods: Patients with cystinuria (n=18), comprised of 10 males and 8 females was studied. The extract of Levisticum officinal eat a dose of one tablespoon, two times a day for two weeks period were prescribed for each individual. Before and after clinical trial, urine volume and cysteine and creatinine, for a period of 24 hours was measured. Demographic, clinical and pharmacological data were recorded in Excel and analyzed using SPSS (version 18) for windows.

Results: There was a positive history of familial cystinuria in 66.7% of total population studied. With a standard deviation of 11.9, the mean age of patients was 34.6 year old. There was a significant decrease before and after administration of Levisticum officinale in urine's level of cysteine (164.3 ± 27.3 versus 108.9 ± 22 mg/dl; p= 0.02). The volume of urine was significantly (p= 0.03) decreased from 1686.1 ± 204.1to1530.5 ± 180.9ml before and after treatment procedure. With values of (1.18 ± 0.37versus1.09 ± 0.32 mg/dl) before and after clinical trial, the changes in urine creatinine tend to be trend (p= 0.09). There was a significant negative correlation between body mass index (BMI) and the level of urine cystine (p = 0.04, r= -0.42).

Conclusions: However within the small number of patients studied, the significantly decreased level in urine cysteine, creatinine and volume might be a clue for possible nephro protective and litolytic properties of Levisticum officinale (Lovage), but in order to confirm such efficacy, further studies in a large number of patients with cystinuria recommended.

ABBREVIATIONS

BMI: Body Mass Index; COLA: Cystine Ornithine Lysine and Arginine; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; FDA: U.S. Food and Drug Administration SD: Standard Deviation

INTRODUCTION

Cystinuria, the typical inherent fault of metabolism, could be categorized by a particular proximal renal tubular flaw, that disturbing cystine, ornithine, lysine, and arginine (COLA) re absorption, which can lead to uroliths and urinary impairment [1,2]. Publications reported, a prevalence of 1:7000 [3,4] and a typical age of onset that was linked to the second decade of life [3]. Due to the poor solubility of cysteine, patients with cystinuria are predisposing to recurrent nephrolithiasis [5]. Nephrolithiasis is related to chronic kidney disease (CKD) and is accountable for 2 to 3% of cases of end-stage renal disease (ESRD).Typically it could be connected to nephrocalcinosis, or a monogenic disorders such ascystinuria [6]. The frequency of cystine stone among urinary tract stone diseases, distinguished as 1-2% and 6-8% in adults and children respectively [7]. A recent publication confirmed that

due to dietary changes, metabolic abnormalities, climate change, and genitourinary abnormalities, the rate of pediatric urolithiasis has been increased [8]. In addition to the long-term risk for renal function impairment, renal colic and recurrent episodes of renal stone are the major morbidities related to cystinuria [9]. The main approach toward disease management, could be considered as the prevention of stone formation, that include hydration, low sodium diet, urinary alkalization with oral agents such as potassium citrate and thiol drugs such as D-penicillamine and tiopronin [10,11]. There are evidences that due to adverse effects of available pharmacological agents and socioeconomic situation most of patients have poor compliance [12,13]. The results of a cohort study indicated that 62.4% of patients with cystinuria were compliant with recommended treatments and therefore, they suggested multimodal management based on strict and regular follow up schedule [14].

In addition to the recommended chemical drugs, there are growing bodies of evidences regarding to the effectiveness of herbal therapy due to the reduced side effects, lower cost and better compliance [15,16].

Several studies have indicated the protective effect of some herbs due to ant oxidative activity in preventing the urolithiatic renal cell damage, by inhibitory activity against crystallization [17]. The herbaceous plant from the Apiaceae family, Levisticum officinale *(Lovage)* mentioned as a kind of herbs which could be used for renal stones [18-20].

Asthe evidences are available since 4thcentury, Levisticum officinale *(Lovage)* has been used for different medical conditions such as cystitis, colic, jaundice, bronchitis and many other diseases. It is also used as a diuretic [21].

However the U.S. Food and Drug Administration (FDA) have recognized Levisticum officinale *(Lovage)* as a safe agent for human consumption, but there are not any well-designed animal or human clinical investigations that evaluate its' proper dose and effectiveness on kidney stones [22]. By considering that urine cystine measurement is an important biochemical marker for both diagnosis and treatment follow up strategy [23], therefore the aim of this study was to investigate the impact of Levisticum officinale (Lovage) on urine cystine level among patients with cystinuria.

MATERIALS AND METHODS

Patients with cystinuria, those referred to the urology clinic of Isfahan Alzahra hospital, conducted to Isfahan Kidney Transplantation Research Center (IKTC) were studied. The study was approved by the regional ethics committee of Isfahan University of Medical Sciences under the research project number of 393023.

In order to select patients with cystinuria, the medical records of individuals who had surgical procedure for renal stones within a year were reviewed (n= 250). Subsequently, frothy patients were nominated for further study, but after explaining treatment plan, only 18 patients were agreed for such strategy and signed the consent form. Therefore, baseline characteristics such as age, weight, BMI, familial history of cystinuria, prescribed drugs for studied population (n=18), were recorded using a questionnaire form. The extract of Levisticum officinale (Lovage) in the form of oral liquid (Zardband Pharmaceuticals Company) was administrated to each individual with a dose of one table spoon, two times a day, for a period of two weeks. A 24 hour urine sample was collected by each patient and the level of cystine, creatinine and urine volume was measured at baseline and after trial. During clinical trial a weekly follow-up was performed and any reported complication was evaluated and recorded. For 24-h urine collection the selected patients were trained by a laboratory staff. The 24-h urinary excretion of cystine was measured using high performance liquid chromatography (**HPLC**) **method. Urine** creatinine **level was measured using** the Jaffe method (Pars Azmoon Co, Tehran-Iran). The data were recorded in Excel and the analyses were performed using the Statistical Package for Social Sciences software, version 18 (SPSS Inc., Chicago, Illinois, USA). Where it was possible, mean ± standard deviation (SD) reported for data. Chi-square and Student's t test were used to compare qualitative and quantitative variables. A p value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Results

Table (1) summarizes the patient characteristics. With a minimum of 8 and a maximum of 58, the mean age of patients was 34.6 ± 11.9 (mean ± SD) year old. Calculated BMI was 26.5 ± 3.36 kg/m^2. There was a familial history of cystinuria in 66.7% of total population studied. The occurrence of cysteine stone was distinguished in 72.2 % of patients. Pharmacotherapy used potassium, D-penicillamine and captopril was verified as positive in 77.8%, 38.9% and 11.1% of patients, correspondingly. (Table 2) shows urine creatinine, urine volume and the level of cystine before and after the administration of Levisticum officinale

Table 1: Patients Characteristics.

Mean ± SD	Variables
Age(yrs)	34.6± 11.98
Sex(male/female)	10/8
Height(cm)	157.5±13.98
Weight(kg)	66.28± 2.96
Body Mass Index(kg/m$^{2)}$	26.45± 3.36
Familiar history of cystinuria; n (%)	12(66.7%)
Occurrence ofcystine stone	14 (77.2%)
Pharmacotherapy used: Potassium D-penicillamine Captopril	 14(77.8%) 7(38.9%) 2(11.1%)

Table 2: Urine creatinine, urine volume and the level of cystine before and after the administration of Levisticum officinale *(Lovage)* in patients with cystinuria.

Variables	Before	After	*p value*
Urine creatinine(mg/dl)	1.18± 0.37	1.09± 0.32	0.09
Urine volume(ml)	1686.1 ± 204.1	1530.5 ±180.9	0.03
Urine cystine (mg/dl)	164.3 ± 27.3	108.9±22	0.02

(Lovage) in patients with cystinuria. As shown in (Figure 1), with a p value of 0.09, there was tendency to decrease in serum creatinine (mg/dl) with values of 1.18 ±0.37 *versus* 1.09 ± 0.32 before and after administration of Levisticum officinale respectively. (Figure 2) demonstrates a significant decrease (*p = 0.02*) in urine cystine (mg/dl) with values of: 164.3 ± 27.3 *versus* 108.9 ± 22.0 before and after clinical trial respectively. There was a decrease in the volume of urine (ml) before and after the treatment process, with a significant p value of 0.03, as was detailed from 1686.1 ± 204.31 *versus* 1530.5 ± 180.9 in that order. There was a significant decrease (*p = 0.03*) related to the reduction in urine cysteine (mg/dl) according to the genders, as was expressed to, 96.9 ± 34.6 in males *versus* 3.4 ± 27.1 in females. There was not any significant relationship between the age and the level of urine cystine (*p=0.37*) in each individual. There was a significant negative correlation between BMI and the level of urine cystine (*p=0.04, r=-0.42*). Not complications were reported among studied population.

Discussion

Cystinuria is a rare inherited disease with increased urinary excretion of the poorly soluble amino acid cysteine [24]. Genetic factors such as SLC3A1 and SLC7A9 seem to play an important role in patients with such disease. In this case renal tubules are not capable for reabsorbing cystine and its' relative insolubility at physiological urine pH could lead to stone formation [25].

Many publications suggested that keystone of the management should be based on stoppage of stone formation with hyper hydration, urinary alkalization, and appropriate pharmacotherapy [13,25]. Therefore remedy to decrease stone formation should be managed in the direction of dropping urine cystine concentration and increasing cystine solubility [1-25].

In this trial after two weeks administration of Levisticum officinale (Lovage), which has been recommended in traditional medicine of Iran besides [26], there was a significant decrease on the level of cysteine, creatinine and urine volume, among patients with cystinuria.

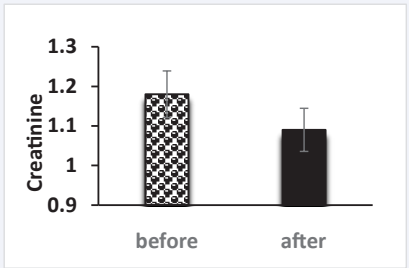

Figure 1 Urine creatinine (mg/dl) before and after administration of Levisticum officinale (n=18; p =0.09).

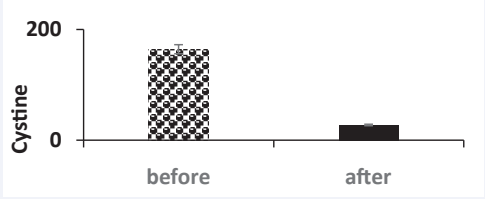

Figure 2 Urine cystine (mg/dl) before and after admnisatration of Levisticum offinale (n=18; p=0.02).

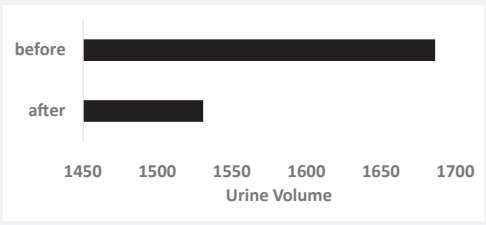

Figure 3 Urine voulme (ml) before and after administration of Levisicum officinal (n=18 =0.03).

Due to recurrence of stone formation and non-obedience of patients to recommended treatment, management of cystinuria should be considered as a challenging issue. Also the adverse effects of pharmacological agents seem to be as one of the major causes of unpleasant strategy both for patients and clinicians [12,13].

Levisticumofficinale (Lovage) is from the large plant family of Apiaceae and its different medical properties have been reported in traditional medicine [27]. All parts of the plant could be used for various medical purposes. The most important constituents of Levisticum officinale (Lovage) are polyacetylenes which consist of 3(R)-falcarinol and 3(R)-8(S)-falcarindiol that was demonstrated to have many bioactivities [28-30]. Its bioactive secondary metabolites are essential oils, polyphenols (flavonoids, phenolic acids), coumarins (furano- and pyranocoumarins), saponins, alkaloids and polyacetylenes [27]. There are reports regarding the spasmolytic and diuretic effects of Levisticum officinale (Lovage) [16,22]. Moreover, it is recommended for lower urinary tract infections and urinary gravel by German Commission E [31]. The Natural Standard Research Collaboration published a report regarding different properties of Levisticum officinale (Lovage) such asits' preventative effect for renal stones [32].

Levisticumofficinale (Lovage) is one of the component of Canephron® N (CAN) that is recommended for prophylaxis and treatment of urinary tract infections in both adults and children, renal stones in adults, prevention of urinary tract infections and other gestational diseases in pregnancy.

Naber et al., in 2013, reviewed the clinical experiences of CAN in Eastern Europe and Central Asia. They suggested that a ten day add-on therapy of CAN could have improving effect on spontaneous elimination of kidney stones compared with standard therapy alone as well as stone prevention [33].

In agreement with Naber et al., in 2013 in this study, after a two weeks trial related to Levisticum officinale (Lovage) administration, the level of cystine decreased significantly which indicate its possible nephro protective and litolytic properties.

Worcester et al., in 2008 confirmed that cystinuria could be defined based on the 24h urine cystine excretion. Therefore cystine excretion of more than> 400mg/dl could result to a recurrent stone formation. The recommended level of urine

cystine concentration is lower than 240mg/dl [33]. By keeping its concentration below the recommended level, the cystine super saturation would be prevented.

Considering that the population studied, have had a history of surgery due to cystine stones at least for one occasion, it could be suggested that prescribing Levisticum officinale (Lovage) at the initial phase of disease diagnosis could have more appropriate effect.

The negative significant correlation between BMI and level of urine cystine might indicate more significant efficacy of Levisticum officinale (Lovage) in patients with normal weight.

In this study there was not any report of complication or incompliance. This might point to Levisticum officinale (Lovage) safety's with minor adverse effects' when compare to available conventional strategy based on chemical pharmacological agents.

However the result of this study was established for the first time that could be mentioned as the strength of the current investigation, but its' limitation was the small size of sample, absence of control group and lack of long term patients' follow up.

In conclusion, the outcomes of the current clinical trial in patients with cystinuria pointed out that Levisticum officinale (Lovage) might have a proper effect on urine cysteine. Therefore it might give the impression as a safe agent that might be able to exhibit protective and positive clinical impact on reducing morbidities related to cystinuria and recurrence of cystine stones formation.

Further studies related to pharmacotherapy used Levisticum officinale (Lovage) in a large number of patients with cystinuria recommended to be advantageous.

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Cite this article

Mohammadi M, Parvaneh E, Tolou-Ghamari Z (2016) Clinical Investigation of Levisticum officinale (Lovage) Effectiveness' in Patients with Cystinuria. J Urol Res 3(6): 1071.